US007711402C1

(12) EX PARTE REEXAMINATION CERTIFICATE (8374th)

United States Patent
Shults et al.

(10) **Number: US 7,711,402 C1**
(45) **Certificate Issued: Jun. 28, 2011**

(54) **DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS**

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Reexamination Request:
No. 90/011,345, Nov. 19, 2010

Reexamination Certificate for:

Patent No.:	**7,711,402**
Issued:	**May 4, 2010**
Appl. No.:	**11/021,046**
Filed:	**Dec. 22, 2004**

Certificate of Correction issued Oct. 12, 2010.

Related U.S. Application Data

(60) Continuation of application No. 09/447,227, filed on Nov. 22, 1999, which is a division of application No. 08/811,473, filed on Mar. 4, 1997, now Pat. No. 6,001,067.

(51) **Int. Cl.**
A61B 5/00 (2006.01)

(52) **U.S. Cl.** **600/347**; 600/365

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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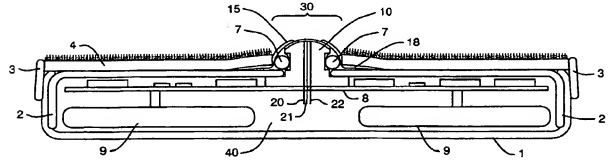
Primary Examiner—Cary E. Wehner

(57) **ABSTRACT**

Devices and methods for determining analyte levels are described. The devices and methods allow for the implantation of analyte-monitoring devices, such as glucose monitoring devices, that result in the delivery of a dependable flow of blood to deliver sample to the implanted device. The devices comprise a unique microarchitectural arrangement in the sensor region that allows accurate data to be obtained over long periods of time.



EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **1** and **23** are cancelled.

Claims **9**, **12**, **17-20**, **22**, **26**, **29** and **34-37** are determined to be patentable as amended.

New claims **39-71** are added and determined to be patentable.

Claims **2-8**, **10**, **11**, **13-16**, **21**, **24**, **25**, **27**, **28**, **30-33** and **38** were not reexamined.

9. The device of claim **[1]** *39*, further comprising an enzyme layer comprising a catalyst.

12. The device of claim **[1]** *39*, wherein the sensing mechanism comprises an enzymatic mechanism.

17. The device of claim **[1]** *39*, wherein the period of time is greater than 4 days.

18. The device of claim **[1]** *39*, wherein the period of time is greater than 5 days.

19. The device of claim **[1]** *39*, wherein the period of time is greater than 6 days.

20. The device of claim **[1]** *39*, wherein the period of time is greater than 7 days.

22. The device of claim **[1]** *39*, wherein the membrane has a thickness of from about 40 microns to about 60 microns.

26. The device of claim **[23]** *54*, wherein the membrane further comprises an enzyme layer comprising a catalyst.

29. The device of claim **[23]** *54*, wherein the sensing mechanism comprises an enzymatic mechanism.

34. The device of claim **[23]** *54*, wherein the useful life of the device is greater than 4 days.

35. The device of claim **[23]** *54*, wherein the useful life of the device is greater than 5 days.

36. The device of claim **[23]** *54*, wherein the useful life of the device is greater than 6 days.

37. The device of claim **[23]** *54*, wherein the useful life of the device is greater than 7 days.

39. A device for measuring glucose in a bodily fluid, the device comprising:

a sensing mechanism operably connected to an electronic circuit and configured to continuously measure a signal associated with a glucose concentration in a host for a period of time greater than 3 days, the sensing mechanism comprising a working electrode, a counter electrode, and a reference electrode, wherein the working electrode, the counter electrode, and the reference electrode are exposed on a single continuous substrate surface, and wherein the working electrode, the counter electrode, and the reference electrode are configured for implantation in a subcutaneous tissue of the host; and

a membrane disposed on a portion of the sensing mechanism, wherein the device is configured to provide at least two phases of sensor function, wherein the at least two phases comprise:

a first phase that occurs after implantation of the device in the subcutaneous tissue and during which the signal provides a substantially unstable measurement of the glucose concentration in the host; and

a second phase that occurs after the occurs after the first phase and during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host, wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood,

wherein the device is configured to respond substantially linearly to changes in glucose concentration at a glucose concentration of up to about 500 mg/dL.

40. The device of claim 39, further comprising an electrolyte layer, wherein the electrolyte layer comprises a flexible, hydrophilic material.

41. The device of claim 39, further comprising a resistance layer comprising a semipermeable membrane configured to control a flux of oxygen and glucose therethrough.

42. The device of claim 39, further comprising a housing filled with a material comprising a resin, wherein the resin secures the electronic circuit within the housing.

43. The device of claim 39, further comprising an apparatus operatively connected to the electronic circuit for transmitting data to a location external to the device.

44. The device of claim 43, wherein the electronic circuit transmits data at intervals.

45. The device of claim 39 further comprising a housing comprising a cavity contained therewithin.

46. The device of claim 45, wherein the sensing mechanism is within the housing cavity.

47. The device of claim 39, further comprising an interference layer configured to restrict the passage of interfering species therethrough.

48. The device of claim 39, wherein the device is configured to provide stable glucose measurements for at least about 90 days after implantation of the device in vivo.

49. The device of claim 39, wherein the sensing mechanism comprises a non-enzymatic mechanism.

50. The device of claim 39, wherein the sensing mechanism comprises a resonance mechanism.

51. The device of claim 39, wherein the sensing mechanism comprises an acoustic wave mechanism.

52. The device of claim 39, wherein the sensing mechanism comprises an optical mechanism.

53. The device of claim 39, wherein the device is configured to provide stabilization of the membrane to reduce motion artifact.

54. A device for measuring glucose in a bodily fluid, the device comprising:

a sensing mechanism configured to generate a signal associated with a concentration of glucose in a host, wherein the sensing mechanism comprises a working electrode, a counter electrode, and a reference electrode, wherein the working electrode, the counter electrode, and the reference electrode are exposed on a single continuous substrate surface, and wherein the working electrode, the counter electrode, and the reference electrode are configured for implantation in subcutaneous tissue of the host; and

a membrane disposed on a portion of the sensing mechanism, wherein the membrane comprises a resistance layer comprising a semipermeable membrane that controls a flux of oxygen and glucose therethrough, wherein the membrane has a thickness of from about 40 microns to about 60 microns;

wherein the device, while implanted in the subcutaneous tissue of the host, is configured to respond substantially linearly to changes in glucose concentration at a glucose level up to 500 mg/dL, wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the reference values are determined by analysis of blood.

55. The device of claim 54, wherein the device further comprises an apparatus configured to transmit data to a location external to the device.

56. The device of claim 54, wherein the membrane further comprises an electrolyte layer, wherein the electrolyte layer comprises a flexible, hydrophilic material.

57. The device of claim 54, wherein the membrane further comprises an interference layer configured to restrict passage of interfering species therethrough.

58. The device of claim 54, wherein the device is configured to provide stable glucose measurements for at least about 90 days after implantation of the device in vivo.

59. The device of claim 54, wherein the sensing mechanism comprises a non-enzymatic mechanism.

60. The device of claim 54, wherein the sensing mechanism comprises a resonance mechanism.

61. The device of claim 54, wherein the sensing mechanism comprises an acoustic wave mechanism.

62. The device of claim 54, wherein the sensing mechanism comprises an optical mechanism.

63. The device of claim 54, wherein the device is configured to provide stabilization of the membrane to reduce motion artifact.

64. The device of claims 1, 23, 39, or 54, wherein the device is configured to account for sensor response time by calculating the glucose concentration at times of reference blood sampling by time shifting sensor data.

65. The device of claims 1, 23, 39, or 54, wherein the device is capable of exhibiting no more than a 10% drop in sensor output at 400 mg/dL over an oxygen concentration change from a pO_2 of 150 mmHg to a pO_2 of 30 mm Hg.

66. The device of claims 1, 23, 39, or 54, wherein at least 95% of glucose concentration values measured by the signal are within 15% of one or more reference values over the useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood.

67. The device of claims 1, 23, 39, or 54, wherein at least 95% of glucose concentration values measured by the signal are within 5% of one or more reference values over the useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood.

68. The device of claims 1, 23, 39, or 54, further comprising electronic circuitry operably connected to the sensing mechanism and configured to calibrate sensor data using preimplant calibration information.

69. The device of claim 68, wherein the electronic circuitry is configured to use a single preimplant calibration.

70. The device of claims 1, 23, 39, or 54, further comprising electronic circuitry operably connected to the sensing mechanism and configured to perform a calibration check during the useful life of the device.

71. The device of claims 1, 23, 39, or 54, further comprising electronic circuitry operably connected to the sensing mechanism and configured to periodically perform recalibration by adjusting a sensor gain.

* * * * *

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/011,345	11/19/2010	7711402	ADCI-GEN48	8372

68851 7590 04/26/2011

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EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 04/26/2011

Please find below and/or attached an Office communication concerning this application or proceeding.

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THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS

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East Palo Alto, CA 94303

Date: 4-26-11

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. : 90011345
PATENT NO. : 7711402
ART UNIT : 3993

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified ex parte reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the ex parte reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Notice of Intent to Issue Ex Parte Reexamination Certificate	Control No.	Patent Under Reexamination	
	90/011,345	7711402	
	Examiner	Art Unit	
	Cary E. Wehner	3993	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

1. ☒ Prosecution on the merits is (or remains) closed in this *ex parte* reexamination proceeding. This proceeding is subject to reopening at the initiative of the Office or upon petition. *Cf.* 37 CFR 1.313(a). A Certificate will be issued in view of
   - (a) ☒ Patent owner's communication(s) filed: *14 March 2011*.
   - (b) ☐ Patent owner's late response filed: _____.
   - (c) ☐ Patent owner's failure to file an appropriate response to the Office action mailed: _____.
   - (d) ☐ Patent owner's failure to timely file an Appeal Brief (37 CFR 41.31).
   - (e) ☐ Other: _____.

   Status of *Ex Parte* Reexamination:
   - (f) Change in the Specification: ☐ Yes ☒ No
   - (g) Change in the Drawing(s): ☐ Yes ☒ No
   - (h) Status of the Claim(s):
     - (1) Patent claim(s) confirmed: _____.
     - (2) Patent claim(s) amended (including dependent on amended claim(s)): *9,17-20,22,26,29 and 34-37*
     - (3) Patent claim(s) cancelled: *1 and 23*.
     - (4) Newly presented claim(s) patentable: 39-71.
     - (5) Newly presented cancelled claims: _____.
     - (6) Patent claim(s) ☐ previously ☐ currently disclaimed: _____
     - (7) Patent claim(s) not subject to reexamination: 2-8, 10, 11, 13-16, 21, 24, 25, 27, 28, 30-33 and 38.

2. ☒ Note the attached statement of reasons for patentability and/or confirmation. Any comments considered necessary by patent owner regarding reasons for patentability and/or confirmation must be submitted promptly to avoid processing delays. Such submission(s) should be labeled: "Comments On Statement of Reasons for Patentability and/or Confirmation."

3. ☐ Note attached NOTICE OF REFERENCES CITED (PTO-892).

4. ☐ Note attached LIST OF REFERENCES CITED (PTO/SB/08 or PTO/SB/08 substitute.).

5. ☐ The drawing correction request filed on _____ is: ☐ approved ☐ disapproved.

6. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   - ☐ been received.
   - ☐ not been received.
   - ☐ been filed in Application No. _____.
   - ☐ been filed in reexamination Control No. _____.
   - ☐ been received by the International Bureau in PCT Application No. _____.

   * Certified copies not received: _____.

7. ☐ Note attached Examiner's Amendment.

8. ☐ Note attached Interview Summary (PTO-474).

9. ☐ Other: _____.

cc: Requester (if third party requester)

Reexamination

STATEMENT OF REASONS FOR PATENTABILITY AND/OR CONFIRMATION

The following is an examiner's statement of reasons for patentability and/or confirmation of the claims found patentable in this reexamination proceeding:

AK 4/25/11

Regarding claims 39, ~~58~~ 54, 66/1, 66/23, 67/1 and 67/23, the prior art of record does not show or fairly suggest a device for measuring glucose comprising, *inter alia*, a working electrode, a counter electrode and a reference electrode all exposed on a single continuous substrate surface and are configured for implantation of subcutaneous tissue, such that the device has a second phase of sensor function during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood. Neither Jobst nor Moatti-Sirat teaches the accuracy duration claimed for a period of greater than 5 hours. Jobst only shows a duration of 3.5 hours and all of the tests in Moatti-Sirat were only run for a period of 70 minutes (Figure 7).

Regarding claim 64, the prior art of record does not show or fairly suggest a device for measuring glucose comprising, *inter alia*, a working electrode, a counter electrode and a reference electrode all exposed on a single continuous substrate surface and are configured for implantation of subcutaneous tissue, such that the device

has a second phase of sensor function during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device, and wherein the one or more reference values are determined by analysis of blood and the device is configured to account for sensor response time by calculating the glucose concentration at times of reference blood sampling by time shifting sensor data.

Regarding claim 65, the prior art of record does not show or fairly suggest a device for measuring glucose comprising, *inter alia*, a working electrode, a counter electrode and a reference electrode all exposed on a single continuous substrate surface and are configured for implantation of subcutaneous tissue, such that the device has a second phase of sensor function during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device, and wherein the one or more reference values are determined by analysis of blood and the device is capable of exhibiting no more than a 10% drop in sensor output at 400 mg/dL over an oxygen concentration change from a pO_2 of 150 mmHg to a pO_2 of 30 mm Hg.

Regarding claim 68/1 and 68/23, the prior art of record does not show or fairly suggest a device for measuring glucose comprising, *inter alia*, a working electrode, a counter electrode and a reference electrode all exposed on a single continuous substrate surface and are configured for implantation of subcutaneous tissue, circuitry

connected to the sensing mechanism and configured to calibrate sensor data using preimplant calibration information, wherein the device has a second phase of sensor function during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device, and wherein the one or more reference values are determined by analysis of blood.

Regarding claim 70/1 and 70/23, the prior art of record does not show or fairly suggest a device for measuring glucose comprising, *inter alia*, a working electrode, a counter electrode and a reference electrode all exposed on a single continuous substrate surface and are configured for implantation of subcutaneous tissue, circuitry connected to the sensing mechanism and configured to perform a calibration check during the useful life of the device, wherein the device has a second phase of sensor function during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device, and wherein the one or more reference values are determined by analysis of blood.

Regarding claim 71/1 and 72/23, the prior art of record does not show or fairly suggest a device for measuring glucose comprising, *inter alia*, a working electrode, a counter electrode and a reference electrode all exposed on a single continuous substrate surface and are configured for implantation of subcutaneous tissue, circuitry

connected to the sensing mechanism and configured to periodically perform recalibration by adjusting a sensor gain, wherein the device has a second phase of sensor function during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device, and wherein the one or more reference values are determined by analysis of blood.

Any comments considered necessary by PATENT OWNER regarding the above statement must be submitted promptly to avoid processing delays. Such submission by the patent owner should be labeled: "Comments on Statement of Reasons for Patentability and/or Confirmation" and will be placed in the reexamination file.

All correspondence relating to this *ex parte* reexamination proceeding should be directed as follows:

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For EFS-Web transmissions, 37 CFR 1.8(a)(1) (i)(C) and (ii) states that correspondence (except for a request for reexamination and a corrected or replacement request for reexamination) will be considered timely filed if: (a) it is transmitted via the Office's electronic filing system in accordance with 37 CFR 1.6(a)(4); and, (b) includes a certificate of transmission for each piece of correspondence stating the date of transmission, which is prior to the expiration of the set period of time in the Office action.

Any inquiry concerning this communication or earlier communications from the Reexamination Legal Advisor or Examiner, or as to the status of this proceeding, should be directed to the Central Reexamination Unit at telephone number (571) 272-7705. The examiner's supervisor is Andres Kashnikow whose phone number is: (571) 272-4361.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

/Cary E. Wehner/
Primary Examiner
Central Reexamination Unit
(571) 272-4715

Conferee 

Conferee 

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent	:	US 7,711,402
Reexam. No	:	90/011,345
Filed	:	11/19/2010
For	:	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS
Examiner	:	Wehner, Cary
Art Unit	:	3993
Conf No.	:	8372

RESPONSE TO OFFICE ACTION

Mail Stop *Ex Parte* Reexam
Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated January 12, 2010, for which a response is due on March 14, 2011, Patent Owner herewith submits a response and respectfully request reconsideration and allowance of the pending claims in light of the remarks presented herein.

Amendment to the Claims begins on page 2 of this paper.

Summary of Interview begins on page 9 of this paper.

Claim Status and Support for Amendments begins on page 10 of this paper.

Remarks begin on page 16 of this paper.

AMENDMENT TO THE CLAIMS

1. (Canceled)

2. (Original) The device of claim 1, further comprising an electrolyte layer, wherein the electrolyte layer comprises a flexible, hydrophilic material.

3. (Original) The device of claim 1, further comprising a resistance layer comprising a semipermeable membrane configured to control a flux of oxygen and glucose therethrough.

4. (Original) The device of claim 1, further comprising a housing filled with a material comprising a resin, wherein the resin secures the electronic circuit within the housing.

5. (Original) The device of claim 1, further comprising an apparatus operatively connected to the electronic circuit for transmitting data to a location external to the device.

6. (Original) The device of claim 5, wherein the electronic circuit transmits data at intervals.

7. (Original) The device of claim 1 further comprising a housing comprising a cavity contained therewithin.

8. (Original) The device of claim 7, wherein the sensing mechanism is within the housing cavity.

9. (Currently Amended) The device of claim 39 [1], further comprising an enzyme layer comprising a catalyst.

10. (Original) The device of claim 1, further comprising an interference layer configured to restrict the passage of interfering species therethrough.

11. (Original) The device of claim 1, wherein the device is configured to provide stable glucose measurements for at least about 90 days after implantation of the device in vivo.

12. (Currently Amended) The device of claim 39 [1], wherein the sensing mechanism comprises an enzymatic mechanism.

13. (Original) The device of claim 1, wherein the sensing mechanism comprises a non-enzymatic mechanism.

14. (Original) The device of claim 1, wherein the sensing mechanism comprises a resonance mechanism.

15. (Original) The device of claim 1, wherein the sensing mechanism comprises an acoustic wave mechanism.

16. (Original) The device of claim 1, wherein the sensing mechanism comprises an optical mechanism.

17. (Currently Amended) The device of claim 39 [1], wherein the period of time is greater than 4 days.

18. (Currently Amended) The device of claim 39 [1], wherein the period of time is greater than 5 days.

19. (Currently Amended) The device of claim 39 [1], wherein the period of time is greater than 6 days.

20. (Currently Amended) The device of claim 39 [1], wherein the period of time is greater than 7 days.

21. (Original) The device of claim 1, wherein the device is configured to provide stabilization of the membrane to reduce motion artifact.

22. (Currently Amended) The device of claim 39 [1], wherein the membrane has a thickness of from about 40 microns to about 60 microns.

23. (Canceled)

24. (Original) The device of claim 23, wherein the device further comprises an apparatus configured to transmit data to a location external to the device.

25. (Original) The device of claim 23, wherein the membrane further comprises an electrolyte layer, wherein the electrolyte layer comprises a flexible, hydrophilic material.

26. (Currently Amended) The device of claim 54 [23], wherein the membrane further comprises an enzyme layer comprising a catalyst.

27. (Original) The device of claim 23, wherein the membrane further comprises an interference layer configured to restrict passage of interfering species therethrough.

28. (Original) The device of claim 23, wherein the device is configured to provide stable glucose measurements for at least about 90 days after implantation of the device in vivo.

29. (Currently Amended) The device of claim 54 [23], wherein the sensing mechanism comprises an enzymatic mechanism.

30. (Original) The device of claim 23, wherein the sensing mechanism comprises a non-enzymatic mechanism.

31. (Original) The device of claim 23, wherein the sensing mechanism comprises a resonance mechanism.

32. (Original) The device of claim 23, wherein the sensing mechanism comprises an acoustic wave mechanism.

33. (Original) The device of claim 23, wherein the sensing mechanism comprises an optical mechanism.

34. (Currently Amended) The device of claim 54 [23], wherein the useful life of the device is greater than 4 days.

35. (Currently Amended) The device of claim 54 [23], wherein the useful life of the device is greater than 5 days.

36. (Currently Amended) The device of claim 54 [23], wherein the useful life of the device is greater than 6 days.

37. (Currently Amended) The device of claim 54 [23], wherein the useful life of the device is greater than 7 days.

38. (Original) The device of claim 23, wherein the device is configured to provide stabilization of the membrane to reduce motion artifact.

39. (New) A device for measuring glucose in a bodily fluid, the device comprising:

a sensing mechanism operably connected to an electronic circuit and configured to continuously measure a signal associated with a glucose concentration in a host for a period of time greater than 3 days, the sensing mechanism comprising a working electrode, a counter electrode, and a reference electrode, wherein the working electrode, the counter electrode, and the reference electrode are exposed on a single continuous substrate surface, and wherein the working electrode, the counter electrode, and the reference electrode are configured for implantation in a subcutaneous tissue of the host; and

a membrane disposed on a portion of the sensing mechanism, wherein the device is configured to provide at least two phases of sensor function, wherein the at least two phases comprise:

a first phase that occurs after implantation of the device in the subcutaneous tissue and during which the signal provides a substantially unstable measurement of the glucose concentration in the host; and

a second phase that occurs after the occurs after the first phase and during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host, wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood,

wherein the device is configured to respond substantially linearly to changes in glucose concentration at a glucose concentration of up to about 500 mg/dL.

40. (New) The device of claim 39, further comprising an electrolyte layer, wherein the electrolyte layer comprises a flexible, hydrophilic material.

41. (New) The device of claim 39, further comprising a resistance layer comprising a semipermeable membrane configured to control a flux of oxygen and glucose therethrough.

42. (New) The device of claim 39, further comprising a housing filled with a material comprising a resin, wherein the resin secures the electronic circuit within the housing.

43. (New) The device of claim 39, further comprising an apparatus operatively connected to the electronic circuit for transmitting data to a location external to the device.

44. (New) The device of claim 43, wherein the electronic circuit transmits data at intervals.

45. (New) The device of claim 39 further comprising a housing comprising a cavity contained therewithin.

46. (New) The device of claim 45, wherein the sensing mechanism is within the housing cavity.

47. (New) The device of claim 39, further comprising an interference layer configured to restrict the passage of interfering species therethrough.

48. (New) The device of claim 39, wherein the device is configured to provide stable glucose measurements for at least about 90 days after implantation of the device in vivo.

49. (New) The device of claim 39, wherein the sensing mechanism comprises a non-enzymatic mechanism.

50. (New) The device of claim 39, wherein the sensing mechanism comprises a resonance mechanism.

51. (New) The device of claim 39, wherein the sensing mechanism comprises an acoustic wave mechanism.

52. (New) The device of claim 39, wherein the sensing mechanism comprises an optical mechanism.

53. (New) The device of claim 39, wherein the device is configured to provide stabilization of the membrane to reduce motion artifact.

54. (New) A device for measuring glucose in a bodily fluid, the device comprising:

a sensing mechanism configured to generate a signal associated with a concentration of glucose in a host, wherein the sensing mechanism comprises a working electrode, a counter electrode, and a reference electrode, wherein the working electrode, the counter electrode, and the reference electrode are exposed on a single continuous substrate surface, and wherein the working electrode, the counter electrode, and the reference electrode are configured for implantation in subcutaneous tissue of the host; and

a membrane disposed on a portion of the sensing mechanism, wherein the membrane comprises a resistance layer comprising a semipermeable membrane that controls a flux of oxygen and glucose therethrough, wherein the membrane has a thickness of from about 40 microns to about 60 microns;

wherein the device, while implanted in the subcutaneous tissue of the host, is configured to respond substantially linearly to changes in glucose concentration at a glucose level up to 500mg/dL, wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the reference values are determined by analysis of blood.

55. (New) The device of claim 54, wherein the device further comprises an apparatus configured to transmit data to a location external to the device.

56. (New) The device of claim 54, wherein the membrane further comprises an electrolyte layer, wherein the electrolyte layer comprises a flexible, hydrophilic material.

57. (New) The device of claim 54, wherein the membrane further comprises an interference layer configured to restrict passage of interfering species therethrough.

58. (New) The device of claim 54, wherein the device is configured to provide stable glucose measurements for at least about 90 days after implantation of the device in vivo.

59. (New) The device of claim 54, wherein the sensing mechanism comprises a non-enzymatic mechanism.

60. (New) The device of claim 54, wherein the sensing mechanism comprises a resonance mechanism.

61. (New) The device of claim 54, wherein the sensing mechanism comprises an acoustic wave mechanism.

62. (New) The device of claim 54, wherein the sensing mechanism comprises an optical mechanism.

63. (New) The device of claim 54, wherein the device is configured to provide stabilization of the membrane to reduce motion artifact.

64. (New) The device of claims 1, 23, 39, or 54, wherein the device is configured to account for sensor response time by calculating the glucose concentration at times of reference blood sampling by time shifting sensor data.

65. (New) The device of claims 1, 23, 39, or 54, wherein the device is capable of exhibiting no more than a 10% drop in sensor output at 400 mg/dL over an oxygen concentration change from a pO_2 of 150 mmHg to a pO_2 of 30 mm Hg.

66. (New) The device of claims 1, 23, 39, or 54, wherein at least 95% of glucose concentration values measured by the signal are within 15% of one or more reference values over the useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood.

67. (New) The device of claims 1, 23, 39, or 54, wherein at least 95% of glucose concentration values measured by the signal are within 5% of one or more reference values over the useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood.

68. (New) The device of claims 1, 23, 39, or 54, further comprising electronic circuitry operably connected to the sensing mechanism and configured to calibrate sensor data using preimplant calibration information.

69. (New) The device of claim 68, wherein the electronic circuitry is configured to use a single preimplant calibration.

70. (New) The device of claims 1, 23, 39, or 54, further comprising electronic circuitry operably connected to the sensing mechanism and configured to perform a calibration check during the useful life of the device.

71. (New) The device of claims 1, 23, 39, or 54, further comprising electronic circuitry operably connected to the sensing mechanism and configured to periodically perform recalibration by adjusting a sensor gain.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

The personal interview was conducted on February 24, 2011 and attended by Examiners Cary E. Wehner, Michael Phillips, and Jimmy Foster, and Patent Owner's representatives Laura Johnson and Paul Lee.

Exhibits and/or Demonstrations

Patent Owner's representatives demonstrated operation of a continuous glucose sensor and monitor.

Identification of Claims Discussed

Claim 1 and 23 of U.S. Patent No. 7,711,402 ("the '402 Patent").

Identification of Art Discussed

Jobst et al., Thin-Film Microbiosensors for Glucose-Lactate Monitoring, Analytical Chemistry, 68:3173-3179 (1996) ("Jobst").

Proposed Amendments, Principal Arguments, and Other Matters

Patent Owner's representatives presented a proposed claim amendment reciting that the useful life of the device occurred when the device is implanted in subcutaneous tissue and that the useful life of the device is greater than 4 or 5 hours. Patent Owner's representative explained (and the Examiners agreed) that the error grid analysis shown in Fig. 8 of Jobst refers to results from an *ex vivo* device, i.e., a device not implanted into the subcutaneous tissue. Patent Owner's representatives further explained (and the Examiner agreed) that the *in vivo* data shown in Fig. 10 of Jobst does not have a duration greater than 4 hours.

Results of Interview

The Examiners agreed that amending the claims to clarify that the useful life of the device is greater than 4 hours or more (i.e., 5 hours) would overcome Jobst. The Examiners further agreed that deleting the term "or more" from the phrase "of up to about 500 mg/dL or more" would not broaden the claims.

CLAIM STATUS AND SUPPORT FOR AMENDMENTS (37 CFR 1.530(e))

1. **Canceled.**

2. **Pending – Unchanged.**

3. **Pending – Unchanged.**

4. **Pending – Unchanged.**

5. **Pending – Unchanged.**

6. **Pending – Unchanged.**

7. **Pending – Unchanged.**

8. **Pending – Unchanged.**

9. **Pending – Amended.** Claim 9 has been amended to depend from claim 39, instead of claim 1, which has been canceled.

10. **Pending – Unchanged.**

11. **Pending – Unchanged.**

12. **Pending – Amended.** Claim 12 has been amended to depend from claim 39, instead of claim 1, which has been canceled.

13. **Pending – Unchanged.**

14. **Pending – Unchanged.**

15. **Pending – Unchanged.**

16. **Pending – Unchanged.**

17. **Pending – Amended.** Claim 17 has been amended to depend from claim 39, instead of claim 1, which has been canceled.

18. **Pending – Amended.** Claim 18 has been amended to depend from claim 39, instead of claim 1, which has been canceled.

19. **Pending – Amended.** Claim 19 has been amended to depend from claim 39, instead of claim 1, which has been canceled.

20. **Pending – Amended.** Claim 20 has been amended to depend from claim 39, instead of claim 1, which has been canceled.

21. **Pending – Unchanged.**

22. **Pending – Amended.** Claim 22 has been amended to depend from claim 39, instead of claim 1, which has been canceled.

23. **Canceled.**

24. **Pending – Unchanged.**

25. **Pending – Unchanged.**

26. **Pending – Amended.** Claim 26 has been amended to depend from claim 54, instead of claim 23, which has been canceled.

27. **Pending – Unchanged.**

28. **Pending – Unchanged.**

29. **Pending – Amended.** Claim 29 has been amended to depend from claim 54, instead of claim 23, which has been canceled.

30. **Pending – Unchanged.**

31. **Pending – Unchanged.**

32. **Pending – Unchanged.**

33. **Pending – Unchanged.**

34. **Pending – Amended.** Claim 34 has been amended to depend from claim 54, instead of claim 23, which has been canceled.

35. **Pending – Amended.** Claim 35 has been amended to depend from claim 54, instead of claim 23, which has been canceled.

36. **Pending – Amended.** Claim 36 has been amended to depend from claim 54, instead of claim 23, which has been canceled.

37. **Pending – Amended.** Claim 37 has been amended to depend from claim 54, instead of claim 23, which has been canceled.

38. **Pending – Unchanged.**

39. **Pending – New.** New Claim 39 recites:

> A device for measuring glucose in a bodily fluid, the device comprising: a sensing mechanism operably connected to an electronic circuit and configured to continuously measure a signal associated with a glucose concentration in a host for a period of time greater than 3 days, the sensing mechanism comprising a working electrode, a counter electrode, and a reference electrode, wherein the working electrode, the counter electrode, and the reference electrode are exposed on a single continuous substrate surface, and wherein the working electrode, the counter electrode, and the reference electrode are configured for implantation in a subcutaneous tissue of the host; and a membrane disposed on a portion of the sensing mechanism, wherein the device is configured to provide at least two phases

> of sensor function, wherein the at least two phases comprise: a first phase that occurs after implantation of the device in the subcutaneous tissue and during which the signal provides a substantially unstable measurement of the glucose concentration in the host; and a second phase that occurs after the occurs after the first phase and during which the signal provides a substantially stable measurement of the glucose concentration in the subcutaneous tissue of the host, wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood, wherein the device is configured to respond substantially linearly to changes in glucose concentration at a glucose concentration of up to about 500 mg/dL

New Claim 39 includes all the limitations present in canceled Claim 1. Additionally, Claim 39 recites that at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host. Support for these limitations can be found, e.g., at Col. 3, Ln. 65 –Col. 4, Ln. 7; and Col. 4, Lns. 18-19 of the '402 Patent.

40. **Pending – New.** New Claim 40 includes the limitations present in unchanged Claim 2.

41. **Pending – New.** New Claim 41 includes the limitations present in unchanged Claim 3.

42. **Pending – New.** New Claim 42 includes the limitations present in unchanged Claim 4.

43. **Pending – New.** New Claim 43 includes the limitations present in unchanged Claim 5.

44. **Pending – New.** New Claim 44 includes the limitations present in unchanged Claim 6.

45. **Pending – New.** New Claim 45 includes the limitations present in unchanged Claim 7.

46. **Pending – New.** New Claim 46 includes the limitations present in unchanged Claim 8.

47. **Pending – New.** New Claim 47 includes the limitations present in unchanged Claim 10.

48. **Pending – New.** New Claim 48 includes the limitations present in unchanged Claim 11.

49. **Pending – New.** New Claim 49 includes the limitations present in unchanged Claim 13.

50. **Pending – New.** New Claim 50 includes the limitations present in unchanged Claim 14.

51. **Pending – New.** New Claim 51 includes the limitations present in unchanged Claim 15.

52. **Pending – New.** New Claim 52 includes the limitations present in unchanged Claim 16.

53. **Pending – New.** New Claim 53 includes the limitations present in unchanged Claim 21.

54. **Pending – New.** New Claim 54 recites:

> A device for measuring glucose in a bodily fluid, the device comprising: a sensing mechanism configured to generate a signal associated with a concentration of glucose in a host, wherein the sensing mechanism comprises a working electrode, a counter electrode, and a reference electrode, wherein the working electrode, the counter electrode, and the reference electrode are exposed on a single continuous substrate surface, and wherein the working electrode, the counter electrode, and the reference electrode are configured for implantation in subcutaneous tissue of the host; and a membrane disposed on a portion of the sensing mechanism, wherein the membrane comprises a resistance layer comprising a semipermeable membrane that controls a flux of oxygen and glucose therethrough, wherein the membrane has a thickness of from about 40 microns to about 60 microns; wherein the device, while implanted in the subcutaneous tissue of the host, is configured to respond substantially linearly to changes in glucose concentration at a glucose level up to 500mg/dL, wherein at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the reference values are determined by analysis of blood.

New Claim 54 includes all the limitations of canceled Claim 23. Additionally, Claim 54 recites that at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host. Support for these limitations can be found, e.g., at Col. 3, Ln. 65 –Col. 4, Ln. 7; and Col. 4, Lns. 18-19 of the '402 Patent.

55. **Pending – New.** New Claim 55 includes the limitations present in unchanged Claim 24.

56. **Pending – New.** New Claim 56 includes the limitations present in unchanged Claim 25.

57. **Pending – New.** New Claim 57 includes the limitations present in unchanged Claim 27.

58. **Pending – New.** New Claim 58 includes the limitations present in unchanged Claim 28.

59. **Pending – New.** New Claim 59 includes the limitations present in unchanged Claim 30.

60. **Pending – New.** New Claim 60 includes the limitations present in unchanged Claim 31.

61. **Pending – New.** New Claim 61 includes the limitations present in unchanged Claim 32.

62. **Pending – New.** New Claim 62 includes the limitations present in unchanged Claim 33.

63. **Pending – New.** New Claim 63 includes the limitations present in unchanged Claim 38.

64. **Pending – New.** New Claim 64 includes the limitation that the device "is configured to account for sensor response time by calculating the glucose concentration at times of reference blood sampling by time shifting sensor data." Support for this limitation can be found, *e.g.*, at Col. 21, Lns. 11-13 of the '402 Patent.

65. **Pending – New.** New Claim 65 includes the limitation that the device "is capable of exhibiting no more than a 10% drop in sensor output at 400 mg/dL over an oxygen concentration change from a pO_2 of 150 mmHg to a pO_2 of 30 mm Hg." Support for this limitation can be found, *e.g.*, at Col. 21, Lns. 34-38 of the '402 Patent.

66. **Pending – New.** New Claim 66 includes the limitation that the device is capable of obtaining an accuracy level corresponding to "at least 95% of glucose concentration values measured by the signal are within 15% of one or more reference values over the useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more

reference values are determined by analysis of blood." Support for this limitation can be found, *e.g.*, at Col. 4, Lns. 32-33 of the '402 Patent.

67. **Pending – New.** New Claim 67 includes the limitation that the device is capable of obtaining an accuracy level corresponding to "at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values over the useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood" Support for this limitation can be found, *e.g.*, at Col. 4, Lns. 32-33 of the '402 Patent.

68. **Pending – New.** New Claim 68 includes the limitation that the device further comprises "electronic circuitry operably connected to the sensing mechanism and configured to calibrate sensor data using preimplant calibration information." Support for this limitation can be found, *e.g.*, at Col. 20, Lns. 32-35; and Col. 21, Lns 10-11 of the '402 Patent.

69. **Pending – New.** New Claim 69 includes the limitation that "the electronic circuitry is configured to use a single preimplant calibration." Support for this limitation can be found, *e.g.*, at Col. 20, Lns. 32-35; and Col. 21, Lns 10-11 of the '402 Patent.

70. **Pending – New.** New Claim 70 includes the limitation that the device further comprises "electronic circuitry operably connected to the sensing mechanism and configured to perform a calibration check during the useful life of the device." Support for this limitation can be found, *e.g.*, at Col. 4, Lns. 33-36 of the '402 Patent.

71. **Pending – New.** New Claim 71 includes the limitation that the device further comprises "electronic circuitry operably connected to the sensing mechanism and configured to periodically perform recalibration by adjusting a sensor gain." Support for this limitation can be found, *e.g.*, at Col. 17, Lns. 28-35 of the '402 Patent.

REMARKS

Claim Status

Claims 1, 9, 12, 17-20, 22, 23, 26, 29, and 34-37 of the '402 Patent were subject to reexamination. By virtue of this Amendment, Claims 1 and 23 have been canceled, Claims 9, 12, 17-20, 22, 26, 29, Claims 34-37 have been amended, and new Claims 39-71 have been added. Accordingly, upon entry of this Amendment, Claims 9, 12, 17-20, 22, 26, 29, 34-37, and 39-71 will be pending and currently under reexamination. Pending Claims 2-8, 10, 11, 13-16, 24, 25, 27, 28, 30, 31-33, and 38 are not subject to reexamination.

Prior Art Rejections

A. Claims 1 and 17-20 are patentable over Jobst

Claims 1 and 17-20 stand rejected under 35 U.S.C. 102(a) as allegedly anticipated by Jobst. The Patent Owner respectfully traverses this anticipatory rejection. "A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." *See, e.g., In re Paulsen*, 31 U.S.P.Q.2d 1671 (Fed. Cir. 1994).

Claim 1 has been canceled and replaced with new Claim 39. New Claim 39 includes all the limitations of canceled Claim 1. Additionally, Claim 39 recites that at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host. Support for these limitations can be found, e.g., at Col. 3, Ln. 65 – Col. 4, Ln. 7; and Col. 4, Lns. 18-19 of the '402 Patent.

To support the Office's contention that Jobst anticipates Claims 1 and 17-20, the Office references FIG. 8 and page 3177 of Jobst and states that "Jobst teaches a second phase during which the signal provides a substantially stable measurement of glucose concentration wherein 97% of glucose concentration values are within 20% of reference values." Office Action dated January 12, 2011, at page 5.

Patent Owner respectfully disagrees with the Office's contention that Jobst discloses an *in vivo* sensing device that meets the accuracy standard and duration recited in the claims. First, as agreed upon by the Examiners during the Examiner Interview of February 24, 2011, FIG. 8 of Jobst refers to data from an *ex vivo* sensing device, which stands in contrast to the implanted *in*

vivo sensing device recited in the pending claims. While Jobst does describe an *in vivo* sensing device, this particular device, as illustrated in FIG. 10 reproduced below, fails to achieve the accuracy level recited in the claims, i.e., an accuracy level corresponding to 95% of glucose concentration values being within 25% of reference values.

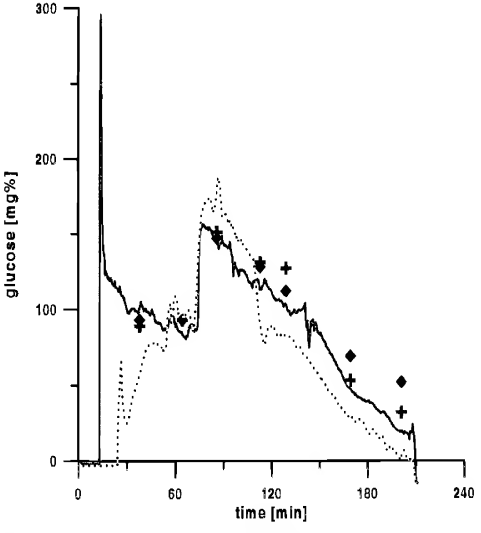

Figure 10. In vivo experiment performed on a pig: —, venous glucose sensor reading; ···, subcutaneous glucose sensor reading; +, Companion2 glucose values; ♦, Hemocue B glucose values. For experimental details, see text.

As illustrated, FIG. 10 of Jobst compares subcutaneous glucose sensor readings with Companion2 glucose values and Hemocue B glucose values, both values of which are based on blood analysis. From what is shown, seven Companion2 glucose values and seven Hemocue B glucose values were collected during the experiment. The last Companion2 glucose value collected (at a time between 180 and 210 minutes) is slightly greater than 50 mg%, and the time-corresponding Hemocue B glucose value collected is slightly greater than 25 mg%. In comparison, the time-corresponding subcutaneous glucose sensor reading appears to be less than 10 mg %. Clearly, both the Companion2 glucose value (greater than 50 mg%) and the Hemocue B glucose value (greater than 25 mg%) are greater than the measured subcutaneous glucose reading (approximately less than 10 mg%). Accordingly, at least one of the seven subcutaneous glucose sensor readings fails to be within 25% of blood glucose reference values. Thus, the data set represented in FIG. 10 in fact shows an accuracy level that is less than a level corresponding to 95% of glucose concentration values measured by the signal being within 25% of one or more reference values. For at least the reason that Jobst fails to disclose an implanted sensing device having an accuracy level corresponding to having at least 95% of glucose concentration values measured by the signal within 25% of one or more reference values, Patent Owner respectfully submits that this anticipatory rejection is improper and thus should be withdrawn.

Second, independent Claim 39, which replaces canceled Claim 1, and from which Claims 17-20 now depend, recites an accuracy duration of greater than 5 hours. Support for these limitations can be found, e.g., at Col. 3, Ln. 65 –Col. 4, Ln. 7; and Col. 4, Lns. 18-19 of the '402 Patent. The experiment corresponding to FIG. 10 of Jobst ran for only about 210 minutes or about 3.5 hours. For at least the reason that Jobst fails to disclose an accuracy duration greater than 5 hours, as recited in Claim 39, Patent Owner submits that this anticipatory rejection cannot stand.

B. Claims 1, 9, 12, and 17-20 are patentable over Jobst in view of Allen

Claims 1, 9, 12, and 17-20 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Jobst in view of Allen. The Patent Owner respectfully traverses this obviousness rejection.

It is well settled that the Examiner "bears the initial burden of presenting a *prima facie* case of unpatentability…" *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). Until the Examiner has established a *prima facie* case of obviousness, Applicants need not present arguments or evidence of non-obviousness. To establish a *prima facie* case of obviousness, the Examiner must establish at least three elements. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02*. And finally, the Examiner must articulate some reason to modify or combine the cited references that renders the claim obvious. Merely establishing that the claimed elements can be found in the prior art is not sufficient to establish a *prima facie* case of obviousness:

> As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added).

Instead, the Court has made clear that the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with

some rational underpinning to support the legal conclusion of obviousness"). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007) (emphasis added).

As explained above, Jobst fails to teach or suggest a device, configured for implantation into the subcutaneous tissue, that can achieve an accuracy level corresponding to having at least 95% of glucose concentration values measured by a sensor signal within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue. Allen also fails to teach or suggest a device with the accuracy level and duration recited in Claim 39, which replaces Claim 1 and from which Claims 9, 12, and 17-20 directly depend. Because Jobst and Allen, even when combined, fail to teach or suggest all limitations of the rejected claims, a *prima facie* case of obviousness cannot be established. For at least this reason, the Patent Owner respectfully submits that this obviousness rejection cannot stand and requests that it be withdrawn.

C. Claim 22 is patentable over Allen in view of Jobst, and further in view of Rhodes

Claim 22 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Allen in view of Jobst, and further in view of Rhodes. The Patent Owner respectfully traverses this obviousness rejection.

The criteria for establishing a *prima facie* case of obviousness are set forth above. As explained above, neither Allen nor Jobst teaches or suggests a device configured for implantation into the subcutaneous tissue that can achieve an accuracy level corresponding to having at least 95% of glucose concentration values measured by a sensor signal within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue. Rhodes also fails to teach or suggest a device with the accuracy level and duration recited in Claim 39, from which Claim 22 depends. Because Allen, Jobst, and Rhodes, even when combined, fail to teach or suggest all limitations of the rejected claims, a *prima facie* case of obviousness cannot be established. For at least this reason, the Patent Owner respectfully submits that this obviousness rejection of Claim 22 cannot stand and requests that it be withdrawn.

D. Claims 22, 23, 26, 29, and 34-37 are patentable over Allen in view of Jobst and Rhodes

Claims 22, 23, 26, 29, and 34-37 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Allen in view of Jobst and Rhodes. The Patent Owner respectfully traverses this obviousness rejection.

Claim 23 has been canceled and replaced with new Claim 54. New Claim 54 includes all the limitations of canceled Claim 23. Additionally, Claim 54 recites that at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host. Support for these limitations can be found, e.g., at Col. 3, Ln. 65 –Col. 4, Ln. 7; and Col. 4, Lns. 18-19 of the '402 Patent.

Pending Claims 22, 26, 29, and 34-37 depend directly on Claims 39 or 54. The criteria for establishing a *prima facie* case of obviousness are set forth above. As explained above, none of Allen, Jobst, or Rhodes teaches or suggests a device, configured for implantation into the subcutaneous tissue, that can achieve an accuracy level corresponding to having at least 95% of glucose concentration values measured by a sensor signal within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue. Because Allen, Jobst, and Rhodes, even when combined, fail to teach or suggest all limitations of the rejected claims, a *prima facie* case of obviousness cannot be established. For at least this reason, the Patent Owner respectfully submits that this obviousness rejection of Claims 22, 26, 29, and 34-37 cannot stand and requests that it be withdrawn.

Dependent Claims Not Subject to Reexamination

Although not subject to reexamination, Patent Owner notes that each of pending Claims 2-8, 10, 11, 13-16, 21, 24, 25, 27, 28, 30-33, and 38 variously depend directly or indirectly from independent Claims 1 or 23. Each of these claims is patentable because it depends from a patentable base claim and for additional patentable features recited therein.

New Claims

New Claims 39-71 have been added.

New independent Claims 39 and 54 includes all the limitations of canceled Claims 1 and 23, respectively. Additionally, Claims 39 and 54 recite that the device is implanted into subcutaneous tissue and that at least 95% of glucose concentration values measured by the signal are within 25% of one or more reference values for a useful life of the device of greater than 5

hours in the subcutaneous tissue of the host. As explained above, none of Allen, Jobst, or Rhodes teaches or suggests a device that is configured for implantation into the subcutaneous tissue of a host and that can achieve an accuracy level corresponding to having at least 95% of glucose concentration values measured by a sensor signal within 25% of one or more reference values for a useful life of the device of greater than 5 hours in the subcutaneous tissue. Because Allen, Jobst, and Rhodes, even when combined, fail to teach or suggest all limitations of the rejected claims, Patent Owner respectfully submits that new Claims 39 and 54 are distinguishable over the cited art of record.

New dependent Claims 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, and 53, which directly or indirectly depend from new Claim 39, include all the limitations present in unchanged Claims 2, 3, 4, 5, 6, 7, 8, 10, 11, 13, 14, 15, 16, and 21, respectively. These claims are patentable for at least the same reasons that Claim 39 is patentable, and are patentable for the unique combination that each dependent claim recites.

New dependent Claims 55, 56, 57, 58, 59, 60, 61, 62, and 63, which directly or indirectly depend from new Claim 54, include all the limitations present in unchanged Claims 24, 25, 27, 28, 30, 31, 32, 33, and 38, respectively. These claims are patentable for at least the same reasons that Claim 54 is patentable, and are patentable for the unique combination that each dependent claim recites.

New dependent Claim 64 recites that the device is "configured to account for sensor response time by calculating the glucose concentration at times of reference blood sampling by time shifting sensor data." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 64 is distinguishable over the art of record.

New dependent Claim 65 recites that the device is "capable of showing no more than a 10% drop in sensor output at 400 mg/dL over an oxygen concentration change from a pO_2 of 150 mmHg to a pO_2 of 30 mm Hg." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 65 is distinguishable over the art of record.

New dependent Claim 66 recites that the device is capable of an accuracy level and duration "wherein at least 95% of glucose concentration values measured by the signal are within 15% of one or more reference values over a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 66 is distinguishable over the art of record.

New dependent Claim 67 recites that the device is capable of an accuracy level and duration "wherein at least 95% of glucose concentration values measured by the signal are within 5% of one or more reference values over a useful life of the device of greater than 5 hours in the subcutaneous tissue of the host, and wherein the one or more reference values are determined by analysis of blood." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 67 is distinguishable over the art of record.

New dependent Claim 68 recites that the device comprises "electronic circuitry operably connected to the sensing mechanism and configured to calibrate sensor data using preimplant calibration information." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 68 is distinguishable over the art of record.

New dependent Claim 69 recites that the device comprises "electronic circuitry configured to use a single preimplant calibration." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 69 is distinguishable over the art of record.

New dependent Claim 70 recites that the device comprises "electronic circuitry operably connected to the sensing mechanism and configured to perform a calibration check during the useful life of the device." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or

suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 70 is distinguishable over the art of record.

New dependent Claim 71 recites that the device comprises "electronic circuitry operably connected to the sensing mechanism and configured to periodically perform recalibration by adjusting a sensor gain." Patent Owner submits that none of Allen, Jobst, or Rhodes teaches or suggests this feature. Accordingly, for at least the reason that none of the cited art of record teaches all the elements of the claim, Patent Owner submits that Claim 70 is distinguishable over the art of record.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Patent Owner is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Patent Owner reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Patent Owner has made any disclaimers or disavowals of any subject matter supported by the present application.

Co-Pending Applications of Assignee

Patent Owner wishes to draw the Examiner's attention to the following applications of the present application's assignee.

Docket No.	Serial No.	Title	Filed
DEXCOM.9CPDVC	07/122395	BIOLOGICAL FLUID MEASURING DEVICE	11/19/1987
DEXCOM.9CPDCP	07/216683	BIOLOGICAL FLUID MEASURING DEVICE	7/7/1988
DEXCOM.008A	08/811473	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	3/4/1997
DEXCOM.008DV1	09/447227	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	11/22/1999

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DEXCOM.8DVCP1	09/636369	SYSTEMS AND METHODS FOR REMOTE MONITORING AND MODULATION OF MEDICAL DEVICES	8/11/2000
DEXCOM.006A	09/916386	MEMBRANE FOR USE WITH IMPLANTABLE DEVICES	7/27/2001
DEXCOM.007A	09/916711	SENSOR HEAD FOR USE WITH IMPLANTABLE DEVICE	7/27/2001
DEXCOM.8DVCP2	09/916858	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	7/27/2001
DEXCOM.010A	10/153356	TECHNIQUES TO IMPROVE POLYURETHANE MEMBRANES FOR IMPLANTABLE GLUCOSE SENSORS	5/22/2002
DEXCOM.024A	10/632537	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	8/1/2003
DEXCOM.026A	10/633329	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	8/1/2003
DEXCOM.016A	10/633367	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	8/1/2003
DEXCOM.025A	10/633404	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	8/1/2003
DEXCOM.011A	10/646333	OPTIMIZED SENSOR GEOMETRY FOR AN IMPLANTABLE GLUCOSE SENSOR	8/22/2003
DEXCOM.012A	10/647065	POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES	8/22/2003
DEXCOM.027A	10/648849	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	8/22/2003
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DEXCOM.028A	10/695636	SILICONE COMPOSITION FOR BIOCOMPATIBLE MEMBRANE	10/28/2003
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DEXCOM.037A	10/789359	INTEGRATED DELIVERY DEVICE FOR CONTINUOUS GLUCOSE SENSOR	2/26/2004

DEXCOM.045A	10/838658	IMPLANTABLE ANALYTE SENSOR	5/3/2004
DEXCOM.044A	10/838909	IMPLANTABLE ANALYTE SENSOR	5/3/2004
DEXCOM.043A	10/838912	IMPLANTABLE ANALYTE SENSOR	5/3/2004
DEXCOM.012CP1	10/842716	BIOINTERFACE MEMBRANES INCORPORATING BIOACTIVE AGENTS	5/10/2004
DEXCOM.8DV1CP	10/846150	ANALYTE MEASURING DEVICE	5/14/2004
DEXCOM.048A	10/885476	SYSTEMS AND METHODS FOR MANUFACTURE OF AN ANALYTE-MEASURING DEVICE INCLUDING A MEMBRANE SYSTEM	7/6/2004
DEXCOM.019A	10/896637	ROLLED ELECTRODE ARRAY AND ITS METHOD FOR MANUFACTURE	7/21/2004
DEXCOM.021A	10/896639	OXYGEN ENHANCING MEMBRANE SYSTEMS FOR IMPLANTABLE DEVICES	7/21/2004
DEXCOM.020A	10/896772	INCREASING BIAS FOR OXYGEN PRODUCTION IN AN ELECTRODE SYSTEM	7/21/2004
DEXCOM.023A	10/897312	ELECTRODE SYSTEMS FOR ELECTROCHEMICAL SENSORS	7/21/2004
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DEXCOM.030A	10/991353	AFFINITY DOMAIN FOR ANALYTE SENSOR	11/16/2004
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DEXCOM.031A	11/007635	SYSTEMS AND METHODS FOR IMPROVING ELECTROCHEMICAL ANALYTE SENSORS	12/7/2004
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DEXCOM.007C1	11/021162	SENSOR HEAD FOR USE WITH IMPLANTABLE DEVICES	12/22/2004
DEXCOM.040A	11/034343	COMPOSITE MATERIAL FOR IMPLANTABLE DEVICE	1/11/2005

DEXCOM.039A	11/034344	IMPLANTABLE DEVICE WITH IMPROVED RADIO FREQUENCY CAPABILITIES	1/11/2005
DEXCOM.024C1	11/038340	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	1/18/2005
DEXCOM.8DVCP2C	11/039269	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	1/19/2005
DEXCOM.034A	11/055779	BIOINTERFACE MEMBRANE WITH MACRO- AND MICRO-ARCHITECTURE	2/9/2005
DEXCOM.051A8	11/077643	TRANSCUTANEOUS ANALYTE SENSOR	3/10/2005
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DEXCOM.051A4	11/077713	TRANSCUTANEOUS ANALYTE SENSOR	3/10/2005
DEXCOM.051A6	11/077714	TRANSCUTANEOUS ANALYTE SENSOR	3/10/2005
DEXCOM.051A	11/077715	TRANSCUTANEOUS ANALYTE SENSOR	3/10/2005
DEXCOM.051A10	11/077739	TRANSCUTANEOUS ANALYTE SENSOR	3/10/2005
DEXCOM.051A11	11/077740	TRANSCUTANEOUS ANALYTE SENSOR	3/10/2005
DEXCOM.050A	11/077759	TRANSCUTANEOUS MEDICAL DEVICE WITH VARIABLE STIFFNESS	3/10/2005
DEXCOM.051A7	11/077763	METHOD AND SYSTEMS FOR INSERTING A TRANSCUTANEOUS ANALYTE SENSOR	3/10/2005
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DEXCOM.061CP1	11/334107	TRANSCUTANEOUS ANALYTE SENSOR	1/17/2006
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DEXCOM.061CP4	11/360819	ANALYTE SENSOR	2/22/2006
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DEXCOM.075A	11/404417	SILICONE BASED MEMBRANES FOR USE IN IMPLANTABLE GLUCOSE SENSORS	4/14/2006
DEXCOM.010CP1	11/404418	SILICONE BASED MEMBRANES FOR USE IN IMPLANTABLE GLUCOSE SENSORS	4/14/2006
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DEXCOM.060A	11/413238	CELLULOSIC-BASED RESISTANCE DOMAIN FOR AN ANALYTE SENSOR	4/28/2006
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DEXCOM.060A1	11/413356	CELLULOSIC-BASED RESISTANCE DOMAIN FOR AN ANALYTE SENSOR	4/28/2006
DEXCOM.051C1	11/415593	TRANSCUTANEOUS ANALYTE SENSOR	5/2/2006
DEXCOM.011DV3	11/415631	OPTIMIZED SENSOR GEOMETRY FOR AN IMPLANTABLE GLUCOSE SENSOR	5/2/2006
DEXCOM.051C3	11/415999	TRANSCUTANEOUS ANALYTE SENSOR	5/2/2006
DEXCOM.011DV1	11/416058	OPTIMIZED SENSOR GEOMETRY FOR AN IMPLANTABLE GLUCOSE SENSOR	5/2/2006
DEXCOM.011DV2	11/416346	OPTIMIZED SENSOR GEOMETRY FOR AN IMPLANTABLE GLUCOSE SENSOR	5/2/2006
DEXCOM.051C2	11/416375	TRANSCUTANEOUS ANALYTE SENSOR	5/2/2006
DEXCOM.012CP1C2	11/416734	BIOINTERFACE MEMBRANES INCORPORATING BIOACTIVE AGENTS	5/3/2006
DEXCOM.012CP1C1	11/416825	BIOINTERFACE MEMBRANES INCORPORATING BIOACTIVE AGENTS	5/3/2006
DEXCOM.051CP4	11/439559	ANALYTE SENSOR	5/23/2006
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DEXCOM.61CP3CP1	11/445792	ANALYTE SENSOR	6/1/2006
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DEXCOM.51CP3CP1	11/503367	ANALYTE SENSOR	8/10/2006
DEXCOM.27CP1CP2	11/515342	SYSTEMS AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	9/1/2006
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DEXCOM.088A	11/543396	ANALYTE SENSOR	10/4/2006

DEXCOM.088A3	11/543404	ANALYTE SENSOR	10/4/2006
DEXCOM.088A2	11/543490	ANALYTE SENSOR	10/4/2006
DEXCOM.038CP2	11/543539	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	10/4/2006
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DEXCOM.038CP1	11/543707	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	10/4/2006
DEXCOM.038CP4	11/543734	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	10/4/2006
DEXCOM.8DCP2CC1	11/546157	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	10/10/2006
DEXCOM.012DV1	11/654135	POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES	1/17/2007
DEXCOM.058CP1	11/654140	MEMBRANES FOR AN ANALYTE SENSOR	1/17/2007
DEXCOM.058CP2	11/654327	MEMBRANES FOR AN ANALYTE SENSOR	1/17/2007
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DEXCOM.61CP2CP1	11/690752	TRANSCUTANEOUS ANALYTE SENSOR	3/23/2007
DEXCOM.088CP3	11/691424	ANALYTE SENSOR	3/26/2007
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DEXCOM.088CP2	11/691432	ANALYTE SENSOR	3/26/2007
DEXCOM.088CP4	11/691466	ANALYTE SENSOR	3/26/2007
DEXCOM.38CP1CP1	11/692154	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	3/27/2007
DEXCOM.61CP2CP4	11/734178	TRANSCUTANEOUS ANALYTE SENSOR	4/11/2007
DEXCOM.61CP2CP2	11/734184	TRANSCUTANEOUS ANALYTE SENSOR	4/11/2007
DEXCOM.61CP2CP3	11/734203	TRANSCUTANEOUS ANALYTE SENSOR	4/11/2007
DEXCOM.093A	11/750907	ANALYTE SENSORS HAVING A SIGNAL-TO-NOISE RATIO SUBSTANTIALLY UNAFFECTED BY NON-CONSTANT NOISE	5/18/2007
DEXCOM.27CP1CP3	11/762638	SYSTEMS AND METHODS FOR REPLACING SIGNAL DATA ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	6/13/2007

3DEXCOM.028DV1	11/763215	SILICONE COMPOSITION FOR BIOCOMPATIBLE MEMBRANE	6/14/2007
DEXCOM.051C4	11/797520	TRANSCUTANEOUS ANALYTE SENSOR	5/3/2007
DEXCOM.051C5	11/797521	TRANSCUTANEOUS ANALYTE SENSOR	5/3/2007
DEXCOM.061CP2C2	11/842139	TRANSCUTANEOUS ANALYTE SENSOR	8/21/2007
DEXCOM.061C1	11/842142	TRANSCUTANEOUS ANALYTE SENSOR	8/21/2007
DEXCOM.61CP2CPC	11/842143	TRANSCUTANEOUS ANALYTE SENSOR	8/20/2007
DEXCOM.061CP4C1	11/842146	ANALYTE SENSOR	8/20/2007
DEXCOM.061A1C1	11/842148	TRANSCUTANEOUS ANALYTE SENSOR	8/21/2007
DEXCOM.61CP3CPC	11/842149	TRANCUTANEOUS ANALYTE SENSOR	8/21/2007
DEXCOM.077C1	11/842151	ANALYTE SENSOR	8/21/2007
DEXCOM.061CP2C1	11/842154	TRANSCUTANEOUS ANALYTE SENSOR	8/21/2007
DEXCOM.093C1	11/842156	ANALYTE SENSORS HAVING A SIGNAL-TO-NOISE RATIO SUBSTANTILALLY UNAFFECTED BY NON-CONSTANT NOISE	8/21/2007
DEXCOM.51P3P1C1	11/842157	ANALYTE SENSOR	8/21/2007
DEXCOM.096A	11/855101	TRANSCUTANEOUS ANALYTE SENSOR	9/13/2007
DEXCOM.38CP1CP2	11/865572	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	10/1/2007
DEXCOM.025C1	11/865660	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	10/1/2007
DEXCOM.051A7C1	11/925603	TRANSCUTANEOUS ANALYTE SENSOR	10/26/2007
DEXCOM.8DV1CPD2	12/037812	ANALYTE MEASURING DEVICE	2/26/2008
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DEXCOM.107A	12/054953	ANALYTE SENSOR	3/25/2008
DEXCOM.88CP1CP2	12/055078	ANALYTE SENSOR	3/25/2008
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DEXCOM.88CP1CP1	12/055114	ANALYTE SENSOR	3/25/2008

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DEXCOM.024C1D2	12/098353	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	4/4/2008
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DEXCOM.051A6C3	12/101790	TRANSCUTANEOUS ANALYTE SENSOR	4/11/2008
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DEXCOM.034DV1	12/103594	BIOINTERFACE WITH MACRO- AND MICRO-ARCHITECTURE	4/15/2008
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DEXCOM.094A2	12/133738	INTEGRATED MEDICAMENT DELIVERY DEVICE FOR USE WITH CONTINUOUS ANALYTE SENSOR	6/5/2008
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DEXCOM.051CP3DV	12/250918	ANALYTE SENSOR	10/14/2008
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DEXCOM.029DV3	12/253120	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	10/16/2008
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DEXCOM.098A	12/258235	SYSTEMS AND METHODS FOR PROCESSING SENSOR DATA	10/24/2008
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DEXCOM.099A1	12/258325	SYSTEMS AND METHODS FOR PROCESSING SENSOR DATA	10/24/2008
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DEXCOM.099A	12/258345	SYSTEMS AND METHODS FOR PROCESSING SENSOR DATA	10/24/2008
DEXCOM.007C1DV1	12/260017	SENSOR HEAD FOR USE WITH IMPLANTABLE DEVICES	10/28/2008
DEXCOM.029C1	12/263993	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	11/3/2008
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DEXCOM.88CPP5P3	12/267546	ANALYTE SENSOR	11/7/2008
DEXCOM.88CPP5P2	12/267547	ANALYTE SENSOR	11/7/2008
DEXCOM.88CPP5P1	12/267548	ANALYTE SENSOR	11/7/2008
DEXCOM.051A12C1	12/273359	TRANSCUTANEOUS ANALYTE SENSOR	11/18/2008
DEXCOM.051C6	12/329496	TRANSCUTANEOUS ANALYTE SENSOR	12/5/2008
DEXCOM.038CP2C1	12/335403	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	12/15/2008
DEXCOM.027DV1	12/353787	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	1/14/2009
DEXCOM.027DV2	12/353799	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	1/14/2009
DEXCOM.061C2	12/353870	TRANSCUTANEOUS ANALYTE SENSOR	1/14/2009
DEXCOM.051C7	12/359207	TRANSCUTANEOUS ANALYTE SENSOR	1/23/2009

DEXCOM.100A	12/362194	CONTINUOUS CARDIAC MARKER SENSOR SYSTEM	1/29/2009
DEXCOM.061CP2C3	12/364786	TRANSCUTANEOUS ANALYTE SENSOR	2/3/2009
DEXCOM.101A	12/365683	CONTINUOUS MEDICAMENT SENSOR SYSTEM FOR IN VIVO USE	2/4/2009
DEXCOM.102A2	12/390205	SYSTEMS AND METHODS FOR CUSTOMIZING DELIVERY OF SENSOR DATA	2/20/2009
DEXCOM.102A3	12/390290	SYSTEMS AND METHODS FOR BLOOD GLUCOSE MONITORING AND ALERT DELIVERY	2/20/2009
DEXCOM.102A1	12/390304	SYSTEMS AND METHODS FOR PROCESSING, TRANSMITTING AND DISPLAYING SENSOR DATA	2/20/2009
DEXCOM.061DV1	12/391148	TRANSCUTANEOUS ANALYTE SENSOR	2/23/2009
DEXCOM.051C10	12/393887	TRANSCUTANEOUS ANALYTE SENSOR	2/26/2009
DEXCOM.104A2	12/413166	POLYMER MEMBRANES FOR CONTINUOUS ANALYTE SENSORS	3/27/2009
DEXCOM.104A1	12/413231	POLYMER MEMBRANES FOR CONTINUOUS ANALYTE SENSORS	3/27/2009
DEXCOM.029DV8	12/424391	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	4/15/2009
DEXCOM.029DV7	12/424403	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	4/15/2009
DEXCOM.061A1C2	12/437436	TRANSCUTANEOUS ANALYTE SENSOR	5/7/2009
DEXCOM.029DV9	12/509396	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	7/24/2009
DEXCOM.075DV1	12/511982	SILICONE BASED MEMBRANES FOR USE IN IMPLANTABLE GLUCOSE SENSORS	7/29/2009
DEXCOM.088CP4C1	12/535620	ANALYTE SENSOR	8/4/2009
DEXCOM.037DV1	12/536852	INTEGRATED DELIVERY DEVICE FOR CONTINUOUS GLUCOSE SENSOR	8/6/2009
DEXCOM.095A	12/562011	PARTICLE-CONTAINING MEMBRANE AND PARTICULATE ELECTRODE FOR ANALYTE SENSORS	9/17/2009
DEXCOM.029DV11	12/565156	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	9/23/2009

DEXCOM.029DV12	12/565166	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	9/23/2009
DEXCOM.029DV13	12/565173	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	9/23/2009
DEXCOM.029DV10	12/565180	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	9/23/2009
DEXCOM.029DV14	12/565199	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	9/23/2009
DEXCOM.032DV1DV	12/565205	INTEGRATED RECEIVER FOR CONTINUOUS ANALYTE SENSOR	9/23/2009
DEXCOM.029DV15	12/565231	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	9/23/2009
DEXCOM.029DV16	12/577668	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	10/12/2009
DEXCOM.029C4	12/577690	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	10/12/2009
DEXCOM.029DV17	12/577691	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	10/12/2009
DEXCOM.027C1	12/579339	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	10/14/2009
DEXCOM.027C3	12/579357	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	10/14/2009
DEXCOM.027C2	12/579363	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	10/14/2009
DEXCOM.027C7	12/579374	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	10/14/2009
DEXCOM.027C4	12/579385	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	10/14/2009
DEXCOM.027C5	12/579388	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	10/14/2009
DEXCOM.027C6	12/579392	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	10/14/2009
DEXCOM.044DV1	12/608872	IMPLANTABLE ANALYTE SENSOR	10/29/2009
DEXCOM.040DV1	12/610127	COMPOSITE MATERIAL FOR IMPLANTABLE DEVICE	10/30/2009
DEXCOM.061CP3C1	12/610866	ANALYTE SENSOR	11/2/2009

DEXCOM.038C1	12/619502	CALIBRATION TECHNIQUES FOR A CONTINUOUS ANALYTE SENSOR	11/16/2009
DEXCOM.104C1	12/628095	POLYMER MEMBRANES FOR CONTINUOUS ANALYTE SENSORS	11/30/2009
DEXCOM.088CP3C2	12/630628	ANALYTE SENSOR	12/3/2009
DEXCOM.006C1C1	12/633578	MEMBRANE FOR USE WITH IMPLANTABLE DEVICES	12/8/2009
DEXCOM.025C1C3	12/633654	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/8/2009
DEXCOM.025C1C6	12/636473	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/11/2009
DEXCOM.025C1C9	12/636494	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/11/2009
DEXCOM.025C1C8	12/636540	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/11/2009
DEXCOM.025C1C5	12/636551	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/11/2009
DEXCOM.025C1C7	12/636574	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/11/2009
DEXCOM.025C1C4	12/636584	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/11/2009
DEXCOM.016C2	12/639746	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/16/2009
DEXCOM.026C1	12/639829	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	12/16/2009
DEXCOM.008DV1C3	12/645097	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	12/22/2009
DEXCOM.008DV1C2	12/645270	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	12/22/2009
DEXCOM.053C2	12/683724	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA FOR SENSOR CALIBRATION	1/7/2010
DEXCOM.053C1	12/683755	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA FOR SENSOR CALIBRATION	1/7/2010

DEXCOM.010DV1C1	12/688737	TECHNIQUES TO IMPROVE POLYURETHANE MEMBRANES FOR IMPLANTABLE GLUCOSE SENSORS	1/15/2010
DEXCOM.021C1C1	12/688763	OXYGEN ENHANCING MEMBRANE SYSTEMS FOR IMPLANTABLE DEVICES	1/15/2010
DEXCOM.026DV1	12/690792	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	1/20/2010
DEXCOM.058C1	12/691617	CELLULOSIC-BASED INTERFERENCE DOMAIN FOR AN ANALYTE SENSOR	1/21/2010
DEXCOM.8DCP2CCC	12/696003	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	1/28/2010
DEXCOM.088CP2C1	12/713607	ANALYTE SENSOR	2/26/2010
DEXCOM.104A1CP1	12/718299	POLYMER MEMBRANES FOR CONTINUOUS ANALYTE SENSORS	3/5/2010
DEXCOM.104A1CP2	12/718332	POLYMER MEMBRANES FOR CONTINUOUS ANALYTE SENSORS	3/5/2010
DEXCOM.051A6C4	12/728032	TRANSCUTANEOUS ANALYTE SENSOR	3/19/2010
DEXCOM.051A6C5	12/728060	TRANSCUTANEOUS ANALYTE SENSOR	3/19/2010
DEXCOM.051A6C6	12/728061	TRANSCUTANEOUS ANALYTE SENSOR	3/19/2010
DEXCOM.051A6C7	12/728082	TRANSCUTANEOUS ANALYTE SENSOR	3/19/2010
DEXCOM.51A8C1C1	12/729035	TRANSCUTANEOUS ANALYTE SENSOR	3/22/2010
DEXCOM.51A8C1C2	12/729048	TRANSCUTANEOUS ANALYTE SENSOR	3/22/2010
DEXCOM.051A10C1	12/729058	TRANSCUTANEOUS ANALYTE SENSOR	3/22/2010
DEXCOM.016C3	12/730058	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/23/2010
DEXCOM.051A10C2	12/730072	TRANSCUTANEOUS ANALYTE SENSOR	3/23/2010
DEXCOM.016C4	12/730077	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/23/2010
DEXCOM.016C6	12/730108	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/23/2010

DEXCOM.016C8	12/730123	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/23/2010
DEXCOM.016C9	12/730132	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/23/2010
DEXCOM.016C7	12/730144	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/23/2010
DEXCOM.016C5	12/730152	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/23/2010
DEXCOM.029C5	12/731046	SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSOR	3/24/2010
DEXCOM.032C1C1	12/731965	INTEGRATED RECEIVER FOR CONTINUOUS ANALYTE SENSOR	3/25/2010
DEXCOM.027C8	12/731980	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	3/25/2010
DEXCOM.27CPCPC1	12/732010	SYSTEMS AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/25/2010
DEXCOM.27CPCP3C	12/732097	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	3/25/2010
DEXCOM.038CP2CC	12/748024	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	3/26/2010
DEXCOM.135A	12/748069	METHODS AND SYSTEMS FOR PROMOTING GLUCOSE MANAGEMENT	3/26/2010
DEXCOM.016C10	12/748144	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	3/26/2010
DEXCOM.053C3	12/748154	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA FOR SENSOR CALIBRATION	3/26/2010
DEXCOM.061A1C3	12/749139	TRANSCUTANEOUS ANALYTE SENSOR	3/29/2010
DEXCOM.38CPCPC2	12/749265	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	3/29/2010
DEXCOM.051A9C3	12/749981	TRANSCUTANEOUS ANALYTE SENSOR	3/30/2010
DEXCOM.038C3	12/760358	CALIBRATION TECHNIQUES FOR CONTINUOUS ANALYTE SENSOR	4/14/2010

DEXCOM.038C2	12/760432	CALIBRATION TECHNIQUES FOR A CONTINUOUS ANALYTE SENSOR	4/14/2010
DEXCOM.8DV1C2C1	12/763013	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	4/19/2010
DEXCOM.8DV1C2C2	12/763016	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	4/19/2010
DEXCOM.138A	12/770618	PERFORMANCE REPORTS ASSOCIATED WITH CONTINUOUS SENSOR DATA FROM MULTIPLE ANALYSIS TIME PERIODS	4/29/2010
DEXCOM.016C12	12/772842	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	5/3/2010
DEXCOM.016C11	12/772849	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	5/3/2010
DEXCOM.051A5C1	12/775315	TRANSCUTANEOUS ANALYTE SENSOR	5/6/2010
DEXCOM.051A12C4	12/780606	TRANSCUTANEOUS ANALYTE SENSOR	5/14/2010
DEXCOM.051A12C2	12/780723	TRANSCUTANEOUS ANALYTE SENSOR	5/14/2010
DEXCOM.051A12C3	12/780725	TRANSCUTANEOUS ANALYTE SENSOR	5/14/2010
DEXCOM.051A12C5	12/780739	TRANSCUTANEOUS ANALYTE SENSOR	5/14/2010
DEXCOM.051A12C6	12/780759	TRANSCUTANEOUS ANALYTE SENSOR	5/14/2010
DEXCOM.027C9	12/787217	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	5/25/2010
DEXCOM.016C13	12/788125	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	5/26/2010
DEXCOM.027C10	12/789153	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	5/27/2010
DEXCOM.027C11	12/791686	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	6/1/2010
DEXCOM.027C12	12/791791	SYSTEM AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	6/1/2010
DEXCOM.88PP5P5P	12/828967	HOUSING FOR AN INTRAVASCULAR SENSOR	7/1/2010

DEXCOM.156A	12/829264	ANALYTE SENSOR	7/1/2010
DEXCOM.111A	12/829296	ANALYTE SENSORS AND METHODS OF MANUFACTURING SAME	7/1/2010
DEXCOM.111A3	12/829306	ANALYTE SENSORS AND METHODS OF MANUFACTURING SAME	7/1/2010
DEXCOM.111A2	12/829318	ANALYTE SENSORS AND METHODS OF MANUFACTURING SAME	7/1/2010
DEXCOM.157A3	12/829337	CONTINUOUS ANALYTE SENSORS AND METHODS OF MAKING SAME	7/1/2010
DEXCOM.157A	12/829339	CONTINUOUS ANALYTE SENSORS AND METHODS OF MAKING SAME	7/1/2010
DEXCOM.157A2	12/829340	CONTINUOUS ANALYTE SENSORS AND METHODS OF MAKING SAME	7/1/2010
DEXCOM.38CPCPC1	12/838691	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	7/19/2010
DEXCOM.038CP4RE	12/839260	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	7/19/2010
DEXCOM.061CP2C4	12/853235	TRANSCUTANEOUS ANALYTE SENSOR	8/9/2010
DEXCOM.096C1	12/869996	TRANSCUTANEOUS ANALYTE SENSOR	8/27/2010
DEXCOM.038C1C2	12/874031	CALIBRATION TECHNIQUES FOR A CONTINUOUS ANALYTE SENSOR	9/1/2010
DEXCOM.038C1C1	12/874045	CALIBRATION TECHNIQUES FOR A CONTINUOUS ANALYTE SENSOR	9/1/2010
DEXCOM.102A1C3	12/880015	SYSTEMS AND METHODS FOR PROCESSING, TRANSMITTING AND DISPLAYING SENSOR DATA	9/10/2010
DEXCOM.102A1C2	12/880026	SYSTEMS AND METHODS FOR PROCESSING, TRANSMITTING AND DISPLAYING SENSOR DATA	9/10/2010
DEXCOM.102A1C1	12/880031	SYSTEMS AND METHODS FOR PROCESSING, TRANSMITTING AND DISPLAYING SENSOR DATA	9/10/2010
DEXCOM.159A	12/893850	TRANSCUTANEOUS ANALYTE SENSOR	9/29/2010
DEXCOM.38PPDC	12/916289	DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR	10/29/2010
DEXCOM.027D2C1	13/014910	SYSTEM AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	1/27/2011
DEXCOM.027D2C2	13/014929	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	1/27/2011

DEXCOM.027D2D1	13/015208	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	1/27/2011
DEXCOM.027D2D2	13/015245	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	1/27/2011
DEXCOM.011D3C1	13/015950	OPTIMIZED SENSOR GEOMETRY FOR AN IMPLANTABLE GLUCOSE SENSOR	1/28/2011
DEXCOM.027C13	13/023879	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	2/9/2011
DEXCOM.027C14	13/023835	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	2/9/2011
DEXCOM.027C15	13/023776	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	2/9/2011
DEXCOM.027C16	13/024076	SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM	2/9/2011
DEXCOM.016DV3RX	90/010988	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	5/10/2010
DEXCOM.016DV2RX	90/011031	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	6/14/2010
DEXCOM.006ARX	90/011067	MEMBRANE FOR USE WITH IMPLANTABLE DEVICES	6/25/2010
DEXCOM.006C1RX	90/011080	MEMBRANE FOR USE WITH IMPLANTABLE DEVICES	7/2/2010
DEXCOM.051A7RX	90/011086	METHODS AND SYSTEMS FOR INSERTING A TRANSCUTANEOUS ANALYTE SENSOR	7/8/2010
DEXCOM.010X	90/011329	TECHNIQUES TO IMPROVE POLYURETHANE MEMBRANES FOR IMPLANTABLE GLUCOSE SENSORS	11/12/2010
DEXCOM.012X	90/011330	POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES	11/12/2010
DEXCOM.008D1C1X	90/011345	DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS	11/19/2010
DEXCOM.051X	90/011351	TRANSCUTANEOUS ANALYTE SENSOR	11/22/2010

DEXCOM.025RX	95/001038	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	4/17/2008
DEXCOM.024RX	95/001039	SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA	4/17/2008

Conclusion

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 14, 2011

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/011,345	11/19/2010	7711402	ADCI-GEN48	8372

68851 7590 02/25/2011

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EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 02/25/2011

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/011,345*.

PATENT NO. *7711402*.

ART UNIT *3993*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Ex Parte Reexamination Interview Summary	Control No.	Patent Under Reexamination	
	90/011,345	7711402	
	Examiner	Art Unit	
	Cary E. Wehner	3993	

All participants (USPTO personnel, patent owner, patent owner's representative):

(1) *Cary E. Wehner* (3) *Paul Lee*

(2) *Michael Phillips, Jimmy Foster* (4) *Laura Johnson*

Date of Interview: *24 February 2011*

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal (copy given to: 1)☐ patent owner 2)☐ patent owner's representative)

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: _____

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.
Any other agreement(s) are set forth below under "Description of the general nature of what was agreed to..."

Claim(s) discussed: *1 and 23*.

Identification of prior art discussed: *Jobst*.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
See Continuation Sheet.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims patentable, if available, must be attached. Also, where no copy of the amendments that would render the claims patentable is available, a summary thereof must be attached.)

A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION MUST INCLUDE PATENT OWNER'S STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. (See MPEP § 2281). IF A RESPONSE TO THE LAST OFFICE ACTION HAS ALREADY BEEN FILED, THEN PATENT OWNER IS GIVEN **ONE MONTH** FROM THIS INTERVIEW DATE TO PROVIDE THE MANDATORY STATEMENT OF THE SUBSTANCE OF THE INTERVIEW (37 CFR 1.560(b)). THE REQUIREMENT FOR PATENT OWNER'S STATEMENT CAN NOT BE WAIVED. **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

		/Cary E. Wehner/ Primary Examiner Art Unit 3993

cc: Requester (if third party requester)

Continuation of Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Patent Owner's representitive presented a proposed amendement adding that the first and second phases occur when the device is implanted in the subcutaneous tissue and that in the second phase the signal provides a stable meansurement of the glucose concentration (where at least 95% of glucose concentration values measured by the signal are within 25% of a reference value) over a useful life of the device of greater than 4 hours in the subcutaneous tissue. It was pointed out that the error grid analysis shown in Fig. 8 of Jobst refers to the ex vivo experiment described on page 3175 where the device is not implanted in the subcutaneous tissue. The results of the in vivo experiment are shown in Figure 10 and does not indicated any mesuerments taken after 3.5 hours and therefore does not teach accurate measurements taken after 4 hours.. PO representitive also presented a proposed new claim essentially the same as amended claim 1 but deleting the words "about" and "or more" from the phrase "of up to about 500 mg/dL or more". It was agreed that this amendment would not broaden the claim .

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68851 7590 01/12/2011

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/011,345*.

PATENT NO. *7711402*.

ART UNIT *3993*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/011,345	Patent Under Reexamination 7711402	
	Examiner Cary E. Wehner	Art Unit 3993	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☐ Responsive to the communication(s) filed on _____ . b☐ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1,9,12,17-20,22,23,26,29 and 34-37* are subject to reexamination.

1b. ☒ Claims *2-8,10,11,13-16,21,24,25,27,28,30-33 and 38* are not subject to reexamination.

2. ☐ Claims _____ have been canceled in the present reexamination proceeding.

3. ☐ Claims _____ are patentable and/or confirmed.

4. ☒ Claims *1,9,12,17-20,22,23,26,29 and 34-37* are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ The drawings, filed on _____ are acceptable.

7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.

8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of the certified copies have

1☐ been received.

2☐ not been received.

3☐ been filed in Application No. _____ .

4☐ been filed in reexamination Control No. _____.

5☐ been received by the International Bureau in PCT application No. _____.

* See the attached detailed Office action for a list of the certified copies not received.

9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.

10. ☐ Other: _____

cc: Requester (if third party requester)

DETAILED ACTION

Waiver of Patent Owner's Statement

Pursuant to the pilot program "Pilot Program for Waiver of Patent Owner's Statement in *Ex Parte* Reexamination Proceedings", 75 Fed. Reg. 47269 (05 August 2010), a telephone call was placed to patent owner's counsel on December 11, 2010, requesting waiver of the patent owner's statement. Patent owner's counsel agreed to waive the rights to file a patent owner statement under 35 USC 304, and as a reexamination has been ordered (see "the Order Granting Request for *Ex Parte* Reexamination mailed December 16, 2010"), the issuance of this Office action at this time is appropriate.

Submissions

In order to insure full consideration of any amendments, affidavits, declarations or other documents as evidence of patentability, such documents must be submitted in response to the first Office action on the merits (which does not result in a close of prosecution). Submissions after the second Office action on the merits, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116 after final rejection and by 37 CFR 41.33 after appeal, which will be strictly enforced.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be conducted with special dispatch" (37

CFR 1.550(a)). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Notification of Concurrent Proceedings

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. **7,711,402** throughout the course of this reexamination proceeding. Likewise, if present, the third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Amendment in Reexamination Proceedings

Patent Owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c). See MPEP § 2250(IV) for examples to assist in the preparation of proper proposed amendments in reexamination proceedings.

Claim Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim Rejections

Claims 1 and 17-20 are rejected under 35 U.S.C. 102(a) as anticipated by Jobst et al. Jobst describes a device for measuring glucose comprising a sensing mechanism connected to an electronic circuit and configured to continuously measure a signal associated with a glucose concentration for a period of 20 days. The sensing mechanism comprises a working electrode, a counter electrode and a reference electrode (Fig. 2). The electrodes are exposed on a single continuous substrate surface (flexible polyimide carrier). A membrane is disposed on a portion of the sensing mechanism, wherein the device is configured to provide a first phase that occurs after implantation and during which the signal provides an unstable measurement of glucose concentration. Also, Jobst uses an error grid analysis as taught in the Clarke publication[1]. Using this analysis, as shown in Fig. 8 and described on page 3177, Jobst teaches a second phase during which the signal provides a substantially stable measurement of glucose concentration wherein 97% of glucose concentration values

[1] Clarke et al, "Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose", Diabetes Care, Vol. 10, No. 5:622-628 (1987).

are within 20% of the reference value. Further, Jobst teaches that accurate concentration measurements can be made up to about 40 mM (or about 720 mg/dL).

Claims 1, 9, 12 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jobst et al in view of Allen. Allen teaches describes a device for measuring glucose comprising a sensing mechanism connected to an electronic circuit and configured to continuously measure a signal associated with a glucose concentration for a period of 72 hours. The sensing mechanism comprises a working electrode 13, a counter electrode 12 and a reference electrode 14. The electrodes are exposed on a single continuous substrate surface 17. A membrane 20 is disposed on a portion of the sensing mechanism. Jobst describes a device for measuring glucose comprising a sensing mechanism connected to an electronic circuit and configured to continuously measure a signal associated with a glucose concentration for a period of 20 days. The sensing mechanism comprises a working electrode, a counter electrode and a reference electrode (Fig. 2). The electrodes are exposed on a single continuous substrate surface (flexible polyimide carrier). A membrane is disposed on a portion of the sensing mechanism, wherein the device is configured to provide a first phase that occurs after implantation and during which the signal provides an unstable measurement of glucose concentration. Also, Jobst uses an error grid analysis as taught in the Clarke publication[2]. Using this analysis, as shown in Fig. 8 and described on page 3177, Jobst teaches a second phase during which the signal provides a substantially stable measurement of glucose concentration wherein 97% of glucose

concentration values are within 20% of the reference value. Further, Jobst teaches that accurate concentration measurements can be made up to about 40 mM (or about 720 mg/dL). It would have been obvious to one of ordinary skill in the art to replace the membrane of Allen with the membrane of Jobst, in order to provide a more accurate sensor for a longer duration of time. Regarding claims 9 and 12, Allen teaches the sensing mechanism comprises an enzymatic mechanism (glucose oxidase 19) (column 5, lines 28-31).

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Allen in view of Jobst et al as applied to claim 1 above, and further in view of Rhodes. Jobst and Allen teach glucose sensors, as discussed above. Jobst does not disclose the thickness of the membrane. Rhodes teaches modifying the thickness of the membrane of a glucose sensor to achieve desired diffusion characteristics. The preferred thickness is in the range of about 40 to about 70 microns (page 31, second para.) which encompasses the claimed thickness. Rhodes also discloses how to determine the desired characteristic of the membrane material. It would have been obvious to one of ordinary skill in the art at the time the invention was made to form the membrane of Jobst with a thickness of about 60 microns, as taught by Rhodes, in order to achieve a desired diffusion characteristic.

Claims 22, 23, 26, 29 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen in view of Jobst et al and Rhodes. Allen and Jobst teach glucose sensors, as discussed above. Jobst does not disclose the thickness of the

[2] Clarke et al, "Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose", Diabetes

membrane. Rhodes teaches modifying the thickness of the membrane of a glucose sensor to achieve desired diffusion characteristics. The preferred thickness is in the range of about 40 to about 70 microns (page 31, second para.) which encompasses the claimed thickness. Rhodes also discloses how to determine the desired characteristic of the membrane material. It would have been obvious to one of ordinary skill in the art at the time the invention was made to form the membrane of Jobst with a thickness of about 60 microns, as taught by Rhodes, in order to achieve a desired diffusion characteristic. Regarding claims 26 and 29, Allen teaches the sensing mechanism comprises an enzymatic mechanism (glucose oxidase 19) (column 5, lines 28-31).

Information Disclosure Statement

The information disclosure statements (IDS) submitted on December 20, 2010 by the patent owner has been considered by the examiner to the extent required by MPEP 2256. MPEP 2256 states, in part:

> Where patents, publications, and other such items of information are submitted by a party (patent owner or requester) in compliance with the requirements of the rules, **the requisite degree of consideration to be given to such information will be normally limited by the degree to which the party filing the information citation has explained the content and relevance of the information.** The initials of the examiner placed adjacent to the citations on the form PTO/SB/08A and 08B or its equivalent, without an indication to the contrary in the record, do not signify that the information has been considered by the examiner any further than to the extent noted above. (Emphasis added)

Care, Vol. 10, No. 5:622-628 (1987).

All correspondence relating to this *ex parte* reexamination proceeding should be directed as follows:

By EFS:
Registered users may submit via the electronic filing system, EFS-Web, at: https://sportal.uspto.gov/authenticate/authenticateuserlocalepf.html.

By **U.S. Postal Service Mail** to:

Mail Stop *Ex Parte* Reexam
ATTN: Central Reexamination Unit
Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
Central Reexamination Unit

By hand to: Customer Service Window
Randolph Building
401 Dulany St.
Alexandria, VA 22314

For EFS-Web transmissions, 37 CFR 1.8(a)(1) (i)(C) and (ii) states that correspondence (except for a request for reexamination and a corrected or replacement request for reexamination) will be considered timely filed if: (a) it is transmitted via the Office's electronic filing system in accordance with 37 CFR 1.6(a)(4); and, (b) includes a certificate of transmission for each piece of correspondence stating the date of transmission, which is prior to the expiration of the set period of time in the Office action.

Any inquiry concerning this communication or earlier communications from the Reexamination Legal Advisor or Examiner, or as to the status of this proceeding, should be directed to the Central Reexamination Unit at telephone number (571) 272-7705. The examiner's supervisor is Andres Kashnikow whose phone number is: (571) 272-4361.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

/Cary E. Wehner/
Primary Examiner
Central Reexamination Unit
(571) 272-4715

Conferee ____/MWP/__

Conferee ____/JGF/____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/011,345	11/19/2010	7711402	ADCI-GEN48	8372

68851 7590 12/16/2010

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
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IRVINE, CA 92614

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 12/16/2010

Please find below and/or attached an Office communication concerning this application or proceeding.

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(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Edward J. Baba
BOZICEVIC, FIELD & FRANCIS, LLP
1900 University Ave., Suite 200
East Palo Alto, CA 94303

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/011,345*.

PATENT NO. *7711402*.

ART UNIT *3993*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Order Granting / Denying Request For Ex Parte Reexamination	Control No.	Patent Under Reexamination	
	90/011,345	7711402	
	Examiner	Art Unit	
	Cary E. Wehner	3993	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed *19 November 2010* has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)☐ PTO-892, b)☒ PTO/SB/08, c)☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

a) ☐ by Treasury check or,

b) ☐ by credit to Deposit Account No. _____, or

c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

cc:Requester (if third party requester)

DECISION ON REQUEST FOR REEXAMINATION

A substantial new question of patentability affecting claims 1, 9, 12, 17-20, 22, 23, 26, 29 and 34-37 of United States Patent Number 7,711,402 (hereinafter "the '402 patent) is raised by the request for *ex parte* reexamination.

Service of Papers

After filing of a request for *ex parte* reexamination by a third party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings are merged) in the reexamination proceeding in the manner provided in 37 CFR 1.248. The document must reflect service or the document may be refused consideration by the Office. See 37 CFR 1.550(f).

Waiver of Right to File Patent Owner Statement

In a reexamination proceeding, Patent Owner may waive the right under 37 CFR 1.530 to file a Patent Owner Statement. The document needs to contain a statement that Patent Owner waives the right under 37 CFR 1.530 to file a Patent Owner Statement and proof of service in the manner provided by 37 CFR 1.248. If the request for reexamination was made by a third party requester, see 37 CFR 1.550(f). The Patent owner may consider using the following statement in a document waiving the right to file a Patent Owner Statement:

Patent Owner waives the right under 37 CFR 1.530 to file a Patent Owner Statement.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Amendment in Reexamination Proceedings

Patent Owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c). See MPEP § 2250(IV) for examples to assist in the preparation of proper proposed amendments in reexamination proceedings.

Submissions

In order to insure full consideration of any amendments, affidavits, declarations or other documents as evidence of patentability, such documents must be submitted in response to the first Office action on the merits (which does not result in a close of

prosecution). Submissions after the second Office action on the merits, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116 after final rejection and by 37 CFR 41.33 after appeal, which will be strictly enforced.

Notification of Concurrent Proceedings

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,711,402 throughout the course of this reexamination proceeding. Likewise, if present, the third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Substantial New Question

The presence or absence of a "substantial new question of patentability" determines whether or not reexamination is ordered.

For a "substantial new question of patentability" to be present, it is only necessary that :

A) the prior art patents and/or printed publications raise a substantial new question of patentability regarding at least one claim, i.e., the teaching of the (prior art) patents and printed publications is such that a reasonable examiner would consider the teaching to be important in deciding whether or not the claim is patentable; and

B) the same question of patentability as to the claim has not been decided by the Office in a previous examination of the patent or in a final holding of invalidity by the Federal Courts in a decision on the merits involving the claim.

A SNQ may be based solely on old art where the old art is being presented/viewed in a new light, or in a different way, as compared with its use in the earlier concluded examination(s), in view of a material new argument or interpretation in the request. (MPEP 2242).

The substantial new question of patentability (SNQP) is based on:

(1) U.S. Patent No. 5,322,063 to Allen et al, issued June 21, 1994 (hereinafter "Allen"),

(2) Moatti-Sirat et al, "Towards Continuous Glucose Monitoring: In Vivo Evaluation of a Miniaturized Glucose Sensor Implanted for Several Days in Rat Subcutaneous Tissue", Diabetologia, 35:224-230 (1992) (hereinafter "Moatti-Sirat"),

(3) Jobst et al, "Thin Film Microbiosensors for Glucose-Lactate Monitoring", Anal. Chem., 68:3173-3179(1996) (hereinafter "Jobst"),

(4) WIPO Publication No. WO9213271 to Rhodes et al, published August 6, 1992 (hereinafter "Rhodes"), and

(5) U.S. Patent No. 5,165,407 to Wilson et al, issued December 24, 1992 (hereinafter "Wilson").

Additional references cited in the request:

(1) Clarke et al, "Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose", Diabetes Care, Vol. 10, No. 5:622-628 (1987),

Allen, Moatti-Sirat, Clarke, Rhodes and Wilson qualify as prior art under 35 USC 102(b) and Jobst qualifies as prior art under 35USC 102(a).

Moatti-Sirat and Wilson were cited during the prosecution of the application that resulted in the '402 patent but was never used in a rejection against the claims in question.

Jobst and Clarke are new teachings, not previously considered.

Allen and Rhodes were cited during the prosecution of the application that resulted in the '402 patent and were used in a rejection against the claims in question.

The request indicates that the requester considers:

(1) Claims 1, 9, 12 and 17-20 are unpatentable over Allen and Moatti-Sirat.

(2) Claim 22 is unpatentable over Allen, Moatti-Sirat and Rhodes.

(3) Claims 23, 26, 29 and 34-37 are unpatentable over Rhodes, Allen and Moatti-Sirat.

(4) Claims 1, 9, 12 and 17-20 are unpatentable over Allen, Jobst and Wilson.

(5) Claim 22 is unpatentable over Allen, Jobst, Wilson and Rhodes.

(6) Claims 23, 26, 29 and 34-37 are unpatentable over Allen, Rhodes and Jobst.

Prosecution History

The "Reasons for Allowance" (mailed) stated that the claims were allowed for the "sensing device, constructed as recited, that meets both the accuracy standard (95% of the data within 25% of a reference value) and linearity standard (linear up to about 500 mg/dl)".

Therefore, prior patent(s) and/or publication(s) that would teach the "sensing device, constructed as recited, that meets both the accuracy standard (95% of the data within 25% of a reference value) and linearity standard (linear up to about 500 mg/dl)", a teaching not previously considered nor addressed in the prior examination of the patent or a final holding of invalidity by the Federal courts, would be such that a reasonable examiner would consider the new teaching to be important in deciding to allow the claims being considered. Hence, prior art patent(s) and/or publication(s) teaching a sensing device meeting the accuracy standard (95% of the data within 25% of a reference value) and linearity standard (linear up to about 500 mg/dl) could form the proper basis for a substantial new question of patentability.

Determination of Substantial New Question of Patentability

The Allen reference is an old teaching, previously considered and addressed in the prior examination of the '402 patent. However, Allen was not considered in combination with Moatti-Sirat nor Jobst. Therefore, Allen is being considered "in a new light".

The Moatti-Sirat reference was cited in the prior examination of the patent. However, Moatti-Sirat was not applied in any rejection of claims that ultimately became patent claims 1, 9, 12, 17-20, 22, 23, 26, 29 and 34-37 under reexamination. Therefore, Moatti-Sirat is being considered "in a new light".

It is agreed that the Allen reference, taken with Moatti-Sirat, raises an SNQ with respect to claims 1, 9, 12 and 17-20, and further taken with Rhodes, raises an SNQ with respect to claims 22, 23, 26, 29 and 34-37.

The examiner's statement of reasons for patentability indicated that the prior art did not teach a sensing device, constructed as recited, that meets both the accuracy standard (95% of the data within 25% of a reference value) and linearity standard (linear up to about 500 mg/dl. Allen teaches a glucose sensor comprising having a working electrode, a counter electrode, and a reference electrode exposed on a single continuous substrate surface. Request page 21-24 are hereby incorporated by reference for reexamination for their explanation of the teaching provided in Moatti-Sirat that was not present in the prosecution of the application which became the '402 patent,

in particular, Moatti-Sirat uses an error grid analysis as taught in the Clarke publication. Using this analysis, as shown in Fig. 6 and described on page 227, Moatti-Sirat teaches a sensor wherein 99% of glucose concentration values are within 20% of the reference value. Further, Moatti-Sirat teaches that accurate concentration measurements can be made up to about 27 mM (or about 490 mg/dL). There is a substantial likelihood that a reasonable examiner would consider these teachings important in deciding whether or not these claims are patentable.

Accordingly, the Allen reference, taken with Moatti-Sirat, raises an SNQ as to claims 1, 9, 12 and 17-20, and further taken with Rhodes, raises an SNQ with respect to claims 22, 23, 26, 29 and 34-37 which has not been decided in a previous examination of the '402 patent.

It is agreed that the Allen reference, taken with Jobst, raises an SNQ with respect to claims 1, 9, 12 and 17-20, and further taken with Rhodes, raises an SNQ with respect to claims 22, 23, 26, 29 and 34-37.

The examiner's statement of reasons for patentability indicated that the prior art did not teach a sensing device, constructed as recited, that meets both the accuracy standard (95% of the data within 25% of a reference value) and linearity standard (linear up to about 500 mg/dl. Allen teaches a glucose sensor comprising having a working electrode, a counter electrode, and a reference electrode exposed on a single continuous substrate surface. Request page 24-27 are hereby incorporated by

reference for reexamination for their explanation of the teaching provided in Jobst that was not present in the prosecution of the application which became the '402 patent, in particular, Jobst uses an error grid analysis as taught in the Clarke publication. Using this analysis, as shown in Fig. 8 and described on page 3177, Jobst teaches a sensor wherein 97% of glucose concentration values are within 20% of the reference value. Further, Jobst teaches that accurate concentration measurements can be made up to about 40 mM (or about 720 mg/dL). There is a substantial likelihood that a reasonable examiner would consider these teachings important in deciding whether or not these claims are patentable.

Accordingly, the Allen reference, taken with Jobst, raises an SNQ as to claims 1, 9, 12 and 17-20, and further taken with Rhodes, raises an SNQ with respect to claims 22, 23, 26, 29 and 34-37 which has not been decided in a previous examination of the '402 patent.

Scope of Reexamination

Since requester did not request reexamination of claims 2-8, 10, 11, 13-16, 21, 24, 25, 27, 28, 30-33 and 38 and did not assert the existence of a substantial new question of patentability (SNQP) for such claims (see 35 U.S.C. § 311(b)(2); see also 37 CFR 1.915b and 1.923), such claims will not be reexamined. This matter was squarely addressed in *Sony Computer Entertainment America Inc., et al. v. Jon W. Dudas*, Civil Action No. 1:05CV1447 (E.D.Va. May 22, 2006), Slip Copy, 2006 WL

1472462. (Not Reported in F.Supp.2d.) The District Court upheld the Office's discretion to not reexamine claims in an *inter partes* reexamination proceeding other than those claims for which reexamination had specifically been requested. The Court stated:

> To be sure, a party may seek, and the PTO may grant, *inter partes* review of each and every claim of a patent. Moreover, while the PTO in its discretion may review claims for which *inter partes* review was not requested, nothing in the statute compels it to do so. To ensure that the PTO considers a claim for *inter partes* review, § 311(b)(2) requires that the party seeking reexamination demonstrate why the PTO should reexamine each and every claim for which it seeks review. Here, it is undisputed that Sony did not seek review of every claim under the '213 and '333 patents. Accordingly, Sony cannot now claim that the PTO wrongly failed to reexamine claims for which Sony never requested review, and its argument that AIPA compels a contrary result is unpersuasive.

The *Sony* decision's reasoning and statutory interpretation apply analogously to *ex parte* reexamination, as the same relevant statutory language applies to both *inter partes* and *ex parte* reexamination. 35 U.S.C. § 302 provides that the *ex parte* reexamination "request must set forth the pertinency and manner of applying cited prior art to every claim for which reexamination is requested" (emphasis added), and 35 U.S.C.3 § 303 provides that "the Director will determine whether a substantial new question of patentability affecting any claim of the patent concerned is raised by the request..." (Emphasis added). These provisions are analogous to the language of 35 U.S.C. § 311(b)(2) and 35 U.S.C. § 312 applied and construed in *Sony*, and would be construed in the same manner. As the Director can decline to reexamine non-requested claims in an *inter partes* reexamination proceeding, the Director can likewise do so in *ex parte* reexamination proceeding. See *Notice of Clarification of Office Policy*

To Exercise Discretion in Reexamining Fewer Than All the Patent Claims (signed Oct. 5, 2006) 1311 OG 197 (Oct. 31, 2006). See also MPEP § 2240, Rev. 5, Aug. 2006.

Therefore, claims 2-8, 10, 11, 13-16, 21, 24, 25, 27, 28, 30-33 and 38 will not be reexamined in this *ex parte* reexamination proceeding.

Conclusion

For the reasons given above, each of the references cited by the requester raises a substantial new question of patentability with respect to the subject patent. Accordingly, claims 1, 9, 12, 17-20, 22, 23, 26, 29 and 34-37 of the subject patent will be reexamined.

All correspondence relating to this *ex parte* reexamination proceeding should be directed as follows:

By EFS:

Registered users may submit via the electronic filing system, EFS-Web, at: https://sportal.uspto.gov/authenticate/authenticateuserlocalepf.html.

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Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
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By hand to: Customer Service Window
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For EFS-Web transmissions, 37 CFR 1.8(a)(1) (i)(C) and (ii) states that correspondence (except for a request for reexamination and a corrected or replacement request for reexamination) will be considered timely filed if: (a) it is transmitted via the Office's electronic filing system in accordance with 37 CFR 1.6(a)(4); and, (b) includes a certificate of transmission for each piece of correspondence stating the date of transmission, which is prior to the expiration of the set period of time in the Office action.

Any inquiry concerning this communication or earlier communications from the Reexamination Legal Advisor or Examiner, or as to the status of this proceeding, should be directed to the Central Reexamination Unit at telephone number (571) 272-7705. The examiner's supervisor is Andres Kashnikow whose phone number is: (571) 272-4361.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

/Cary E. Wehner/
Primary Examiner
Central Reexamination Unit
(571) 272-4715

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/011,345	11/19/2010	7711402	ADCI-GEN48	8372

68851 7590 12/11/2010

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 12/11/2010

Please find below and/or attached an Office communication concerning this application or proceeding.

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(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

ABBOTT DIABETES CARE INC.
BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVE, SUITE 200
EAST PALO ALTO CA 94303

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/011,345*.

PATENT NO. *7711402*.

ART UNIT *3993*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Ex Parte Reexamination Interview Summary – Pilot Program for Waiver of Patent Owner's Statement	Control No. 90/011,345	Patent For Which Reexamination is Requested 7,711,402
	Examiner Cary Wehner	Art Unit 3993

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

All participants (USPTO official and patent owner):

(1) Renee Preston, CRU Paralegal (3)

(2) Rose Thiessen 40,202 (4)

Date of Telephonic Interview: 12/09/2010.

The USPTO official requested waiver of the patent owner's statement pursuant to the pilot program for waiver of patent owner's statement in *ex parte* reexamination proceedings.*

☒ The patent owner **agreed** to waive its right to file a patent owner's statement under 35 U.S.C. 304 in the event reexamination is ordered for the above-identified patent.

☐ The patent owner **did not agree** to waive its right to file a patent owner's statement under 35 U.S.C. 304 at this time.

The patent owner is not required to file a written statement of this telephone communication under 37 CFR 1.560(b) or otherwise. However, any disagreement as to this interview summary must be brought to the immediate attention of the USPTO, and no later than one month from the mailing date of this interview summary. Extensions of time are governed by 37 CFR 1.550(c).

*For more information regarding this pilot program, see *Pilot Program for Waiver of Patent Owner's Statement in Ex Parte Reexamination Proceedings*, 75 *Fed. Reg.* 47269 (August 5, 2010), available on the USPTO Web site at http://www.uspto.gov/patents/law/notices/2010.jsp.

☐ USPTO personnel were unable to reach the patent owner.

The patent owner may contact the USPTO personnel at the telephone number provided below if the patent owner decides to waive the right to file a patent owner's statement under 35 U.S.C. 304.

Renee Preston (571) 272-1607
Signature and telephone number of the USPTO official who contacted or attempted to contact the patent owner.

cc: Requester (if third party requester)

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REEXAM CONTROL NUMBER	FILING OR 371 (c) DATE	PATENT NUMBER
90/011,345	11/19/2010	7711402

CONFIRMATION NO. 8372

REEXAMINATION REQUEST NOTICE

Edward J. Baba
BOZICEVIC, FIELD & FRANCIS, LLP
1900 University Ave., Suite 200
East Palo Alto, CA 94303

Date Mailed: 11/29/2010

NOTICE OF REEXAMINATION REQUEST FILING DATE

(Third Party Requester)

Requester is hereby notified that the filing date of the request for reexamination is 11/19/2010, the date that the filing requirements of 37 CFR § 1.510 were received.

A decision on the request for reexamination will be mailed within three months from the filing date of the request for reexamination. (See 37 CFR 1.515(a)).

A copy of the Notice is being sent to the person identified by the requester as the patent owner. Further patent owner correspondence will be the latest attorney or agent of record in the patent file. (See 37 CFR 1.33). Any paper filed should include a reference to the present request for reexamination (by Reexamination Control Number).

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/jcmcdougald/

Legal Instruments Examiner
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REEXAM CONTROL NUMBER	FILING OR 371 (c) DATE	PATENT NUMBER
90/011,345	11/19/2010	7711402

CONFIRMATION NO. 8372

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The above-identified request for reexamination has been assigned to Art Unit 3993. All future correspondence to the proceeding should be identified by the control number listed above and directed to the assigned Art Unit.

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1900 University Ave., Suite 200
East Palo Alto, CA 94303

/jcmcdougald/

Legal Instruments Examiner
Central Reexamination Unit 571-272-7705; FAX No. 571-273-9900

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2010-11-19
First Named Inventor	Shults, Mark C.
Art Unit	
Examiner Name	
Attorney Docket Number	ADCI-GEN48

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5165407		1992-11-24	Wilson et al.	
	2	5322063		1994-06-21	Allen et al.	

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	1	WO9213271	WO		1992-08-06	Rhodes et al.		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2010-11-19
	First Named Inventor	Shults, Mark C.
	Art Unit	
	Examiner Name	
	Attorney Docket Number	ADCI-GEN48

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Clarke et al., Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose, Diabetes Care, Vol. 10, No. 5:622-628 (1987)	☐
	2	Jobst et al., Thin-Film Microbiosensors for Glucose-Lactate Monitoring, Anal. Chem., 68:3173-3179 (1996)	☐
	3	Moatti-Sirat et al., Towards continuous glucose monitoring: in vivo evaluation of a miniaturized glucose sensor implanted for several days in rat subcutaneous tissue, Diabetologia, 35:224-230 (1992)	☐

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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2010-11-19
	First Named Inventor	Shults, Mark C.
	Art Unit	
	Examiner Name	
	Attorney Docket Number	ADCI-GEN48

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Edward J. Baba, Reg. No. 52581/	Date (YYYY-MM-DD)	2010-11-19
Name/Print	Edward J. Baba	Registration Number	52,581

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EXHIBIT B

USP 5,322,063

US005322063A

United States Patent [19]

Allen et al.

[11] Patent Number: 5,322,063

[45] Date of Patent: Jun. 21, 1994

[54] **HYDROPHILIC POLYURETHANE MEMBRANES FOR ELECTROCHEMICAL GLUCOSE SENSORS**

[75] Inventors: **Douglas J. Allen; Kirk W. Johnson; Robert S. Nevin,** all of Indianapolis, Ind.

[73] Assignee: **Eli Lilly and Company,** Indianapolis, Ind.

[21] Appl. No.: **771,658**

[22] Filed: **Oct. 4, 1991**

[51] **Int. Cl.**[5] **A61B 5/05**

[52] **U.S. Cl.** **128/635;** 128/634; 204/403; 204/412; 436/817

[58] **Field of Search** 204/403, 412, 415; 128/634, 635; 436/817

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,484,987	11/1984	Gough	204/403
4,759,828	7/1988	Young et al.	204/403
4,816,130	3/1989	Karakelle et al.	128/634
4,890,620	1/1990	Gough	204/403
4,909,908	3/1990	Ross et al.	204/403

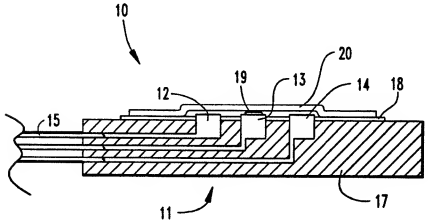
Primary Examiner—Paul Prebilic

Attorney, Agent, or Firm—Woodward, Emhardt, Naughton, Moriarty & McNett

[57] **ABSTRACT**

Homogeneous membranes permeable to oxygen and glucose composed of hydrophilic polyurethanes that are capable of absorbing from 10 to 50% of their dry weight of water. Variations in the composition of the hydrophilic polyurethanes make possible the fabrication of membranes in which the ratios of the diffusion coefficients of oxygen to glucose can be varied over a wide range. These membranes can be used in the fabrication of an electrochemical glucose sensor intended for use in vivo as an aid in the treatment of diabetes mellitus.

15 Claims, 1 Drawing Sheet



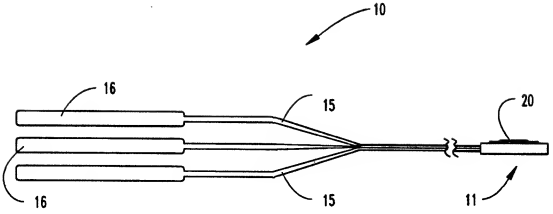


Fig.1

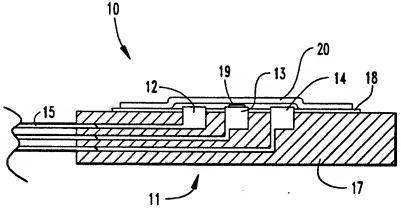


Fig.2

HYDROPHILIC POLYURETHANE MEMBRANES FOR ELECTROCHEMICAL GLUCOSE SENSORS

This invention relates to homogeneous membranes composed of hydrophilic polyurethanes that are useful in the fabrication of electrochemical glucose sensors, particularly those intended for in vivo use.

BACKGROUND OF THE INVENTION

At the present time, there are a number of devices commercially available that allow for external monitoring of glucose levels of urine and blood. These devices, however, do not allow for continuous monitoring, and they require a high degree of patient compliance in order to be effective.

Much research has been directed toward the development of a glucose sensor that would function in vivo as an aid, for example, in the treatment of diabetes mellitus. An implantable glucose sensor that would continuously monitor a patient's blood glucose level could serve as a hypo- and hyperglycemia alarm, and would provide physicians with more accurate information in order to develop optimal therapy. In addition, such a sensor would make possible the development of a "closed loop" insulin delivery system in which a pump delivers insulin as needed, rather than on a programmed basis.

Implantable glucose sensors have been developed based on both optical and electrochemical principles. Schultz and Mansouri have disclosed one version of an optical sensor (J. S. Schultz and S. Mansouri, "Optical Fiber Affinity Sensors," *Methods in Enzymology*, K. Mosbach, Ed., Academic Press, New York, 1988, vol. 137, pp. 349–366). An impediment to the commercial development of an optical sensor of the type disclosed by Schultz and Mansouri has been the difficulty of producing such devices on a commercial basis.

Electrochemical glucose sensors, on the other hand, can be produced using techniques common in the semiconductor industry. The ability to mass produce electrochemical glucose sensors using known commercial techniques gives them a cost advantage over optical sensors. As a consequence, considerable research has been directed toward the development of an in vivo electrochemical glucose sensor. An excellent summary of the issues relating to the development of implantable electrochemical glucose sensors has been published by Turner and Pickup (A. P. F. Turner and J. C. Pickup, "Diabetes Mellitus: Biosensors for Research and Management," *Biosensors*, 1, 85–115 (1985)).

The most favored configuration to date for an electrochemical glucose sensor involves the use of one or two enzymes to catalyze the reaction between glucose and another molecule in order to generate an electrical signal. Typically glucose oxidase is used to catalyze the reaction between glucose and oxygen to yield gluconic acid and hydrogen peroxide, as follows:

$$\text{GLUCOSE} + O_2 \xrightarrow[\text{Oxidase}]{\text{Glucose}} \text{GLUCONIC ACID} + H_2O_2$$

$$H_2O_2 \longrightarrow 2H^+ + O_2 + 2e^-$$

The hydrogen peroxide generated may be detected directly or it may be decomposed by a second enzyme, catalase, in which case the sensor will measure oxygen consumption by the reaction involving glucose oxidase.

The presence of an excess of molecular oxygen, relative to molecular glucose, is necessary for the operation of a glucose oxidase based glucose sensor. This presents a problem in the design of such sensors, since the concentration of oxygen in the subcutaneous tissue is much less than that of glucose. As a consequence, oxygen can become a limiting reactant, giving rise to an "oxygen deficit" problem. Some provision should therefore be made to allow operation of the sensor in an environment with an excess of oxygen.

Many attempts have been made to utilize membranes of various types in an effort to ratio the diffusion of oxygen and glucose to the sensing elements of glucose oxidase based glucose sensors to address the "oxygen deficit" problem. The simplest approach to controlling diffusion has been to use a macroporous or a microporous membrane. For example, in U.S. Pat. No. 4,759,828, Young et al. disclose the use of a laminated membrane with an outer microporous membrane having a pore size of 10 to 125A to limit the diffusion of glucose molecules. One immediate problem with macroporous or microporous membranes, however, is that the sensing element of the sensor is exposed to the environment of the body and is therefore subject to fouling. Young et al. attempted to obviate this problem by the use of a second inner membrane to exclude passage of fouling substances to the sensing element. This design creates additional problems in that transport to the sensing element through the second membrane must not be hindered. Also, because two membranes are necessary, each membrane must be extremely thin so that measurement times are not unduly long.

Another approach has been to utilize a membrane element that contains discrete hydrophilic and hydrophobic domains. In U.S. Pat. No. 4,484,987, Gough discloses a composite membrane in which an immiscible hydrophilic material is physically incorporated in a hydrophobic matrix. The purpose of such a membrane is to achieve a favorable balance between oxygen diffusion through the hydrophobic and hydrophilic matrices and glucose diffusion only through the hydrophilic domains. The effectiveness of such a membrane depends upon the relative amounts of the hydrophilic domains within the hydrophobic matrix. Such membranes are difficult to fabricate reproducibly, particularly on the scale of a glucose sensor meant for implantation within the body. Also, because of the discontinuous nature of the membranes disclosed in Gough '987, physical properties are compromised.

In U.S. Pat. No. 4,890,620, Gough discloses a further elaboration of this concept, utilizing a "two-dimensional" sensing electrode. Here the "membrane" element is physically constructed so that oxygen and glucose diffuse to the sensing electrode at right angles to one another, one direction favoring oxygen diffusion and the other favoring glucose diffusion. While a glucose sensor incorporating the diffusion element of Gough '620 may be useful for research purposes, it would be difficult to fabricate on a commercial scale because of its complexity. Additionally, constraints would be placed upon the size and configuration of the sensor in order to allow for diffusion to the sensing electrode from two directions.

Gernet et al. and Shichiri have recognized the abovementioned difficulties and have utilized a single homogeneous membrane composed of a hydrophobic poly-

urethane (S. Gernet, et al., "Fabrication and Characterization of a Planar Electrochemical Cell and its Application as a Glucose Sensor," *Sensors and Actuators* 18, 59–70 (1989); M. Shichiri, "Glycaemic Control in Pancreatectomized Dogs With a Wearable Artificial Endocrine Pancreas," *Diabetologia*, 24, 179–184 (1983)). While a homogeneous hydrophobic membrane eliminates many of the difficulties mentioned above, it does not provide an optimum balance between oxygen and glucose transport to an electrochemical glucose sensor, nor is it possible to tailor the properties of the homogeneous hydrophobic polyurethane membrane utilized by Gernet et al. and Shichiri to match the design requirements of electrochemical glucose sensors.

SUMMARY OF THE INVENTION

The primary requirement for an electrochemical glucose sensor intended for in vivo use is that the supply of oxygen in the vicinity of the sensing element not be depleted. This does not mean that an electrochemical glucose sensor membrane need have an extremely high permeability to oxygen. What is needed is a membrane that can moderate the diffusion of oxygen and glucose so that the local concentration of oxygen is not depleted. It is sufficient if the ratio of the diffusion coefficient of oxygen to that of glucose is appropriate to the design of the glucose sensor.

Electrochemical glucose sensors intended for in vivo use must also be rendered biocompatible with the body, and they must be able to function in a hostile environment. The enzyme(s) used in such sensors must be protected from degradation or denaturation. At the same time, the sensing elements of such sensors must be protected from molecules which would foul the sensors or their accuracy will decrease over time.

The membranes of the present invention possess unique attributes that satisfy the above objectives. Their properties can be varied to tailor their glucose and oxygen transport behavior to match the requirements of a particular configuration of an electrochemical glucose sensor. The membranes of the present invention are particularly useful in the construction of electrochemical glucose sensors intended for in vivo use.

The homogeneous membranes of the invention are prepared from biologically acceptable polymers whose hydrophobic/hydrophilic balance can be varied over a wide range to control the ratio of the diffusion coefficient of oxygen to that of glucose, and to match this ratio to the design requirements of electrochemical glucose sensors intended for in vivo use.

The membranes of the invention are fabricated from polymers prepared by the reaction of a diisocyanate, a poly(ethylene oxide), and an aliphatic diol. The polymerization reaction may be carried out in solution or in bulk. The preferred hydrophilic polyurethanes so produced are capable of absorbing from about 10 to about 50% of their weight of water, with those capable of absorbing from about 20% to about 30% of their weight of water being preferred. By appropriate selection of the reaction components, membranes can be made from these preferred polymers that exhibit ratios of the diffusion coefficients of oxygen to glucose of up to about 4000, with ratios of about 2000 to about 4000 being preferred.

Since these polymers do not have to be crosslinked in order to develop optimum properties, they are soluble in a variety of solvents and solvent combinations, and thus can be readily fabricated into membranes of various shapes. The membranes of the invention show good adhesion to substrates in an aqueous environment and possess excellent wet-strength. A further advantage of the polymers from which the membranes of the invention are fabricated is that they possess excellent compatibility with the body, a key requirement for an implantable sensor of any type.

It is an objective of the present invention to provide hydrophilic polyurethane membranes for electrochemical glucose sensors to enhance the sensor's biocompatibility and to render the sensor insensitive to changes in the oxygen levels of subcutaneous fluids.

Further and related objects and advantages of the present invention will be apparent from the following description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic view of a glucose sensor having sensor elements with a hydrophilic polyurethane membrane of the present invention secured thereover.

FIG. 2 shows in schematic form an implantable portion of a glucose sensor, with the sensing elements covered with a hydrophilic polyurethane membrane of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to the preferred embodiments and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations and further modifications in the preferred embodiments, and such further applications of the principles of the invention as illustrated thereby being contemplated as would normally occur to one skilled in the art to which the invention relates.

The present invention provides a novel polyurethane membrane for use in covering or encapsulating a glucose sensor, particularly one intended for in vivo use. It has been discovered that the use of such a membrane provides many advantages including control of the glucose and oxygen reactants to permit accurate analysis, protection of the sensor from the hostile in vivo environment, and biocompatibility.

Referring to the drawings, there is shown in schematic form a glucose sensor **10** of typical construction covered or encapsulated with a membrane fabricated in accordance with the present invention. The specific construction and operation of the sensor **10** do not form a part of the present invention. For example, glucose sensors that utilize glucose oxidase to effect a reaction of glucose and oxygen are known in the art, and are within the skill in the art to fabricate. The present invention depends not on the configuration of the sensor, but rather on the use of a hydrophilic polyurethane membrane to cover or encapsulate the sensor elements. Therefore, only a brief description of an exemplary sensor is given herein. Other sensors for monitoring glucose concentration of diabetics are described, for example, in Shichiri, M., Yamasaki, Y., Nao, K., Sekiya, M., Ueda, N.: "In Vivo Characteristics of Needle-Type Glucose Sensor—Measurements of Subcutaneous Glucose Concentrations in Human Volunteers"—Horm. Metab. Res., Suppl. Ser. 20:17–20, 1988; Bruckel, J., Kerner, W., Zier, H., Steinbach, G., Pfeiffer, E.: "In Vivo Measurement of Subcutaneous Glucose Concen-

trations with an Enzymatic Glucose Sensor and a Wick Method," Klin. Wochenschr. 67:491–495, 1989; and Pickup, J., Shaw, G., Claremont, D.: "In Vivo Molecular Sensing in Diabetes Mellitus: An Implantable Glucose Sensor with Direct Electron Transfer," Diabetologia. 32:213–217, 1989.

Sensor **10** includes a distal portion **11** in which are located sensor elements **12–14** which are connected through leads **15** to contacts **16**. Typical sensing elements would be a counter electrode **12**, working electrode **13** and reference electrode **14**. Contacts **16** are connected with a suitable monitoring device (not shown), which receives signals and translates this information into a determination of the glucose level detected.

In this type of sensor, glucose oxidase is also provided in the area adjacent the sensor elements, and catalyzes the reaction of glucose and oxygen. This, or a subsequent reaction, is monitored by the sensing elements, and a determination of glucose present in the surrounding subcutaneous tissue may thereby be obtained.

In one design, the sensor **10** includes a substrate material **17** comprising an electrical insulator. This substrate is preferably flexible to facilitate patient comfort. The counter, working and reference electrodes **12–14** are positioned on the substrate and isolated from one another by an insulation layer **18** patterned to selectively expose the active regions of the three electrodes. Glucose oxidase **19** is deposited on the working electrode and all three sensor/electrodes are then covered with a membrane **20** of the present invention.

The distal portion of the sensor is implanted subcutaneously into the body, and the proximal portion including contacts **16** remains external of the body. In accordance with the present invention, the implanted sensor elements **12–14** are covered with a membrane **20** of the present invention, which controls the rate of diffusion of glucose and oxygen from the surrounding body tissue to the area of the sensor elements. Membrane **20** may fully encapsulate the entire distal portion of the sensor or may simply be layered over the sensor elements. The latter approach may be preferable from the standpoint of ease of fabrication.

The membrane of the invention is formed from a hydrophilic polyurethane. Polyurethane is a thermoplastic polymer produced by the condensation reaction of a polyisocyanate and a hydroxyl-containing material. The membrane is characterized by absorbing from about 10% to about 50%, and preferably from about 20% to about 30%, of its weight in water. Also, the membrane's diffusion coefficient for oxygen should be up to about 4000 times the membrane s diffusion coefficient for glucose, and more preferably between about 2000 and about 4000. Within these preferred ranges, a person skilled in the art can synthesize a variety of suitable polyurethane compositions and readily determine the usefulness of such in the formation of membranes of the present invention.

The preferred membranes of the invention were prepared by the reaction of a diisocyanate with a poly(ethylene oxide) and an aliphatic diol. Preferred diisocyanates include aliphatic diisocyanates containing from 4 to 8 methylene units. In particular, hexamethylene-1,6-diisocyanate has been the most preferred aliphatic diisocyanate in work completed to date. Diisocyanates containing cycloaliphatic moities, such as isophorone diisocyanate and dicyclohexylmethane-4,4'-diisocyanate, may also be used with the latter being the most preferred cycloaliphatic diisocyanate. Aromatic diisocyanates may also be used, but they are less suitable for a medical application because of their extreme toxicity.

The diol component of the polymerization mixture includes a poly(ethylene oxide) and an aliphatic diol. The poly(ethylene oxide) may have an average molecular weight of from 200 to 3000 with a preferred molecular weight range of 600 to 1500, and preferably constitutes about 10 to 50 mole % of the total diol component of the polymerization mixture. Suitable aliphatic diols include ethylene glycol, diethylene glycol, 1,2-propanediol, 1,3-propanediol, and 1,4-butanediol. As will be appreciated by those skilled in the art, other aliphatic diols may be used. These preferred aliphatic diols are chosen for reasons of cost, commercial availability, solubility, reactivity, or ease of purification. The aliphatic diol preferably constitutes about 50 to 90 mole % of the total diol component of the polymerization mixture.

Polymerization was carried out using equimolar quantities of total diol and the diisocyanate. Since the poly(ethylene oxide) is hydrophilic, and the aliphatic diol is hydrophobic, variation in the molar ratio of the two will allow for the preparation of polymers with varying hydrophilic/hydrophobic balances. By a suitable choice of the molar amount and the molecular weight of the poly(ethylene oxide) and the molar amount and specific aliphatic diol, polymers can be prepared that vary from being slightly hydrophilic to very hydrophilic and which can be tailored to have ratios of the diffusion coefficient of oxygen to that of glucose of up to 4000, with ratios of about 2000 to about 4000 being preferred. Polymers having ratios of the diffusion coefficient of oxygen to glucose greater than about 4000 may be too impermeable to glucose and provide too slow a response time. Those membranes with ratios less than about 2000 may result in oxygen deficiency for electrochemical glucose oxidase based sensors.

Polymerization may be carried out in bulk or in a solvent system. Although polymerization may be carried out without a catalyst, the addition of a suitable organometallic compound such as dibutylin bis(2-ethylhexanoate) has been preferred. Bulk polymerization was typically carried out at an initial temperature of about 25° C., typically 50° C., in order to insure adequate mixing of the reactants. Upon mixing of the reactants, an exotherm was typically observed, with the temperature rising to approximately 100° C. After this initial exotherm, the reaction flask was heated at from 75° to 125° C., with 90° to 100° C. being a preferred temperature range. Heating was usually carried out for one to two hours. Solution polymerizations were carried out in a similar manner. Suitable polymerization solvents have been dimethylformamide, dimethyl sulfoxide, dimethylacetamide, halogenated solvents such as 1,2,3-trichloropropane, and ketones such as 4-methyl-2-pentanone. Dimethylformamide has been a preferred solvent. When polymerization was carried out in a solvent, heating of the reaction mixture was typically carried out for three to four hours.

Polymers prepared by bulk polymerization were dissolved in dimethylformamide and precipitated from water. Polymers prepared in solvents that are not miscible with water were isolated by vacuum stripping of the solvent. These polymers were then dissolved in dimethylformamide and precipitated from water. After thor-

oughly washing with water, polymers were dried in vacuo at 50° C. to constant weight.

EXAMPLE I

Typical Procedure for Bulk Polymerization

4.80 g. of poly(ethylene oxide) of molecular weight 600, 2.50 g. of ethylene glycol, and 8.07 g. of hexamethylene-1,6-diisocyanate were charged to a 100 ml. flask. The flask was continually purged with nitrogen. The reaction mixture was heated to 50° C., and then 10 mg. of dibutylin bis(2-ethylhexanoate) dissolved in 7 ml. of 4-methyl-2-pentanone were added to the reaction mixture. The reaction quickly became exothermic, with the temperature rising to 100° C. within a few minutes. The reaction mixture was allowed to cool to 90° C., and it was heated at this temperature for 60 minutes. During this time the reaction mixture changed from a clear viscous liquid to a translucent solid. The polymer was removed from the flask by dissolution in 200 ml. dimethylformamide (90° C.). After cooling to room temperature, the polymer solution was poured into 2 liters of deionized water with vigorous stirring. The precipitated polymer was torn into small pieces and soaked in deionized water for 24 hours, with frequent changes of water. The polymer (number 1 in the Tables) was dried in a vacuum oven at 50° C. to constant weight.

EXAMPLE II

Typical Procedure for Solution Polymerization

14.40 g. of poly(ethylene oxide) (PEO) of molecular weight 600, 12.73 g. of diethylene glycol, 24.22 g. of hexamethylene-1,6-diisocyanate, and 250 ml. of dimethylformamide were added to a 1000 ml. flask. The flask was continually purged with nitrogen. The reaction mixture was heated to 50° C., and 30 mg. of dibutylin bis-(2-ethylhexanoate) dissolved in 25 ml. of 4-methyl-2-pentanone were added to the flask. A slight exotherm caused the temperature to rise to approximately 55° C. The reaction mixture was then heated at 75° C. for 120 minutes and then at 90° C. for another 120 minutes. There was a noticeable increase in viscosity of the reaction mixture during this time. The reaction mixture was diluted with 100 ml. of dimethylformamide and was allowed to cool to room temperature. The solution was poured into 5 liters of vigorously stirred water. The precipitated polymer (number 2 in the Tables) was isolated as in Example I.

Membranes were prepared by casting films from a suitable solvent onto glass using a Gardner knife (Gardner Labs). The solvent chosen will depend on the particular chemical structure of the polymer. Chloroform has been the preferred solvent in work completed to date, since it is readily volatile. Not all polymers of the invention, however, are soluble in this solvent, in which case dimethylformamide has been the preferred solvent. After removal of the solvent, the membranes were hydrated with deionized water for 30–60 minutes. They were then removed and transferred to a Mylar ® support sheet. Wet film thicknesses were measured with a micrometer before removal from the support.

Diffusion constants were measured in a standard permeability cell (Crown Glass Co., Inc.) maintained at 37.0° C., plus or minus 0.1° C., using Fick's relationship:

$$J = -D\,dC/dx$$

where J is total flux, D is the diffusion constant, and dC/dx is the concentration gradient across the membrane.

Oxygen diffusion constants were determined by securing the membrane with two rubber gaskets between the two halves of a diffusion cell maintained at 37.0° C., plus or minus 0.1° C., and clamping the two halves together. Each side of the cell was filled with phosphate buffered saline. One side was saturated with nitrogen while the other side was saturated with air. A calibrated oxygen sensor (Microelectrodes, Inc.) was placed in the nitrogen side of the cell, and measurements were taken at 5 minute intervals until the system reached equilibrium.

Glucose diffusion constants were determined as above except that one half of the cell was filled with phosphate buffered saline containing 300 mg/dl of glucose. The concentration of glucose in each half of the cell was measured at appropriate intervals using a Cooper Assist Clinical Analyzer.

Water pickup was determined on films 4.5 cm. in diameter and less than 0.5 mm. thick at room temperature. After evaporation of the casting solvent, films were dried to constant weight at 50° C. in vacuo. weighed, immersed in deionized water for 24 hours, removed and blotted with filter paper, and weighed. Percent water pickup was determined from the formula

$$\%\ \text{Pickup} = (W_w - W_d)/W_d \times 100$$

where W_w is the weight of the swollen film and W_d is the weight of the dry film.

In accordance with the polymerization reactions of Examples I and II, polymers and resulting membranes may be readily prepared having a wide range of oxygen and glucose diffusion constants and of water pickup. Exemplary compositions were prepared as described in the foregoing Examples, and are identified by composition and % water pickup in Table I. Oxygen and glucose diffusion coefficients, and the ratio of the diffusion coefficient of oxygen to that of glucose, for the resulting membranes are listed in Table II. These formulations demonstrate the ability to vary these parameters over the desired ranges previously described. This control enables one in the art to tailor the membranes to particular glucose sensors.

TABLE I

Polymer	Diisocyanate(M)	Glycol(M)	PEO(M)	Type	% Water Pickup
1	HMDI (0.048)	Ethylene (0.040)	600(0.008)	Bulk	22.0
2	HMDI (0.048)	Diethylene (0.040)	600(0.008)	DMF	24.5
3	HMDI (0.048)	Diethylene (0.040)	1500(0.008)	Bulk	56.0
4	HMDI (0.054)	Diethylene (0.048)	1000(0.006)	Bulk	21.8
5	HMDI (0.052)	Diethylene (0.048)	600(0.004)	Bulk	9.4
6	HMDI (0.052)	Diethylene (0.048)	1000(0.004)	Bulk	15.0
7	MCHI (0.045)	Diethylene (0.042)	1500(0.003)	Bulk	13.4
8	HMDI (0.048)	Diethylene (0.042)	600(0.006)	Bulk	20.0

HMDI = Hexamethylene-1,6-diisocyanate
MCHI = Dicyclohexylmethane-4,4'-diisocyanate

TABLE II

Polymer	D (cm²/sec) Oxygen	D (cm²/sec) Glucose	Ratio DOxygen/DGlucose
1	5.50×10^{-6}	17.4×10^{-8}	32
2	8.83×10^{-6}	2.33×10^{-9}	3790
3	6.93×10^{-6}	7.60×10^{-8}	20
4	4.59×10^{-6}	1.81×10^{-8}	254
5	3.87×10^{-6}	*	—
6	5.72×10^{-6}	3.85×10^{-8}	149
7	4.83×10^{-6}	4.78×10^{-8}	101
8	1.6×10^{-5}	1.1×10^{-8}	1454

* = Impermeable

The preferred membrane identified as Polymer 2 in Tables I and II was evaluated in vitro and in vivo with an amperometric platinum-silver/silver chloride glucose sensor. Information concerning the construction of this sensor has been previously published, R. J. Morff, D. Lipson, K. W. Johnson, J. J. Mastrototaro, C. C. Andrew, A. R. Potvin, "Reproducible Microfabrication of Electroenzymatic Glucose Sensors on a Flexible Substrate," *Proc. 1st World Congress on Biosensors*, (May 2–4, 1990); J. J. Mastrototaro, K. W. Johnson, R. J. Morff, D. Lipson, C. C. Andrew, "An Electroenzymatic Glucose Sensor Fabricated on a Flexible Substrate," *Proc. Third International Meeting on Chemical Sensors*, (Sep. 24–26, 1990), and the disclosures of these publications concerning this sensor are incorporated herein by reference.

The operation of this sensor is based on the reaction of glucose with oxygen in the presence of glucose oxidase to generate hydrogen peroxide. The hydrogen peroxide is subsequently oxidized at the platinum anode, resulting in the generation of a signal that is proportional to glucose concentration.

The membrane was applied over the sensing region. The following in vitro and in vivo evaluations of the coated sensor were then conducted.

In the in vitro testing, a potential of +0.6 V vs. Ag-/AgCl was applied to the working electrode to oxidize the hydrogen peroxide produced by the reaction of glucose and oxygen in the presence of glucose oxidase. The current produced by this reaction was linearly correlated to the amount of glucose present in a test solution.

In order to fully characterize the performance of a glucose sensor designed for implantation in subcutaneous tissue, it was necessary to test not only the sensor's response to changes in the concentration of glucose, but also to changes in the concentration of oxygen. A computer-controlled system was built to automatically expose sixteen sensors provided with membranes of the invention simultaneously to an array of four different glucose concentrations: 0, 100, 200, and 400 mg/dL and four different oxygen concentrations: 1, 2, 5, and 20.9% oxygen (approximately 7–150 mmHg).

Using this system, it was found that the sensors encapsulated in the membrane responded linearly to glucose concentrations ranging from 0–400 mg/dL (correlation coefficient >0.98) and had a very reproducible baseline value in a buffer solution with no glucose. This characteristic of the sensor allowed a one-point calibration to be adequate. In addition, varying the oxygen concentration of the calibration solution between 1 and 20.9% had no effect on the output of the sensor, even at high glucose concentrations. The resolution was better than 10% throughout the entire calibration range and the 90% response time for a change in the glucose concentration from 0 to 100 mg/dL was less than 90 seconds.

A long-term evaluation was also performed whereby the sensors were continuously exposed to a glucose solution (100 mg/dL) at 37° C. for 72 hours. The current output from the sensors was stable, drifting less than 10% over the duration, which demonstrated the sensors' ability to function as continuous monitors for at least three days.

In in vivo testing completed to date, the animal model utilized for study was the New Zealand White Rabbit. The rabbit was surgically equipped with venous and arterial cannulas to allow infusion of fluids and withdrawal of arterial blood samples for analysis.

Prior to implantation in the subcutaneous tissue, the sensor encapsulated in the membrane was inserted into a polyethylene or Teflon ® cannula. Single and double lumen cannulas have been utilized successfully. Stainless steel needle stock was inserted into the cannula to provide rigidity during insertion. This stock may be left in the cannula or removed following implantation to allow more flexibility. A connector was attached to the sensor and sutured to the skin under local anesthetic.

A standard glucose tolerance test was conducted whereby a glucose bolus was given intravenously. An arterial blood presample and samples at 1, 2, 5, 10, 30, and 60 minutes following the injection were collected. This type of test was useful for determining the lag time between a glucose bolus injection into a vein and the peak glucose level in the subcutaneous tissue as indicated by the sensor. An average lag time of 10 minutes was found, which is thought to be a physiologic phenomenon related to the time required for the diffusion of glucose through the capillary wall to the subcutaneous tissue.

A more definitive test, the glucose clamp test, was also conducted. This test involved either elevating or reducing the rabbit's blood glucose level by continuously infusing glucose or insulin. The rate of change in the blood glucose level of the rabbit was slower for a glucose clamp test compared to a tolerance test, making it a test that more closely mimics actual physiologic diabetic conditions. In addition, elevated or reduced glucose levels could be maintained for the period of time necessary for the plasma and subcutaneous glucose values to reach steady-state. This allowed a direct comparison between sensor output and plasma glucose levels.

An excellent correlation between the plasma and subcutaneous tissue glucose values was established. The results from these tests indicated that the sensor provided with a membrane of the present invention will satisfactorily respond to changes in the plasma glucose concentration from as low as 40 mg/dL to in excess of 400 mg/dL, in vivo.

The membranes of the present invention are readily formulated to optimize the diffusion and water pickup characteristics for a given glucose sensor. Membranes of the present invention having water pickups of about 10%, 30% and 50% have been evaluated. In addition, the inventive membranes having oxygen to glucose diffusion ratios of about 1000, 2000 and 3000 perform acceptably in the foregoing circumstances.

While the invention has been described in the foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiments have been described and that all changes and modifications that

come within the spirit of the invention are desired to be protected.

What is claimed is:

1. A homogeneous membrane and an electrochemical glucose sensor combination, said electrochemical glucose sensor including means for evaluating the reaction of glucose and oxygen, said membrane adapted to control the diffusion of glucose and oxygen to the sensor elements, said membrane comprising a hydrophilic polyurethane composition comprising the product of the reaction mixture of:

a diisocyanate selected from the group consisting of hexamethylene-1,6-diisocyanate, dicyclohexylmethane 4,4'-diisocyanate, and isophorone diisocyanate, and constituting about 50 mole % of the reaction mixture;

a poly(ethylene oxide) having an average molecular weight of about 600 to about 1500; and

an aliphatic diol selected from the group consisting of ethylene glycol, diethylene glycol, 1,2-propanediol, 1,3-propanediol, and 1,4-butanediol,

said membrane having an equilibrium water content of about 10% to about 50% and having a ratio of its diffusion coefficient for oxygen to its diffusion coefficient for glucose of up to about 4000, the poly(ethylene oxide) and aliphatic diol components constitute a total diol content of the reaction mixture the total diol content of the reaction mixture comprising from about 10% to about 50% poly(ethylene oxide) and from about 50% to about 90% aliphatic diol.

2. The device of claim 1 wherein the aliphatic diol is diethylene glycol.

3. The device of claim 1 wherein the poly(ethylene oxide) has an average molecular weight of about 600.

4. The device of claim 1 wherein the diisocyanate is hexamethylene-1,6-diisocyanate.

5. The device of claim 4 wherein the aliphatic diol is diethylene glycol.

6. The device of claim 5 wherein the poly(ethylene oxide) has an average molecular weight of about 600.

7. An implantable device for determining the level of glucose in a body, which device comprises:

an electrochemical glucose sensor including means for evaluating the reaction of glucose and oxygen, the evaluating means including sensor elements, and

a membrane secured to said glucose sensor covering the sensor elements and adapted to control the diffusion of glucose and oxygen to the sensor elements, said membrane comprising a hydrophilic polyurethane composition comprising the product of the reaction mixture of:

a diisocyanate selected from the group consisting of hexamethylene-1,6-diisocyanate, dicyclohexylmethane 4,4'-diisocyanate, and isophorone diisocyanate, and constituting about 50 mole % of the reaction mixture;

a poly(ethylene oxide) having an average molecular weight of about 600 to about 1500; and

an aliphatic diol selected from the group consisting of ethylene glycol, diethylene glycol, 1,2-propanediol, 1,3-propanediol, and 1,4-butanediol,

said membrane having an equilibrium water content of about 10% to about 50% and having a ratio of its diffusion coefficient for oxygen to its diffusion coefficient for glucose of up to about 4000, the poly(ethylene oxide) and aliphatic diol components constitute a total diol content of the reaction mixture the total diol content of the reaction mixture comprising from about 10% to about 50% poly(ethylene oxide) and from about 50% to about 90% aliphatic diol.

8. The device of claim 7 in which the aliphatic diol is diethylene glycol.

9. The device of claim 7 in which the poly(ethylene oxide) has an average molecular weight of about 600.

10. The device of claim 8 in which the diisocyanate is hexamethylene-1,6-diisocyanate.

11. The membrane of claim 1 wherein said device has an equilibrium water content of about 20% to about 30%.

12. The membrane of claim 1 in which said device has a ratio of its diffusion coefficient for oxygen to its diffusion coefficient for glucose of about 2000 to about 4000.

13. The membrane of claim 12 wherein said device has an equilibrium water content of about 20% to about 30%.

14. The device of claim 7 wherein said membrane has an equilibrium water content of about 20% to about 30%.

15. The device of claim 7 in which said membrane has a ratio of its diffusion coefficient for oxygen to its diffusion coefficient for glucose of about 2000 to about 4000.

* * * * *

EXHIBIT C

"THE MOATTI-SIRAT PUBLICATION"

Diabetologia (1992) 35: 224–230

Diabetologia

Towards continuous glucose monitoring: in vivo evaluation of a miniaturized glucose sensor implanted for several days in rat subcutaneous tissue

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Summary. A miniaturized amperometric, enzymatic, glucose sensor (outer diameter 0.45 mm) was evaluated after implantation in the subcutaneous tissue of normal rats. A simple experimental procedure was designed for the long-term assessment of the sensor's function which was performed by recording the current during an intraperitoneal glucose load. The sensor was calibrated by accounting for the increase in the current during the concomitant increase in plasma glucose concentration, determined in blood sampled at the tail vein. This made it possible to estimate the glucose concentration in subcutaneous tissue. During the glucose load, the change in subcutaneous glucose concentration followed that in blood with a lag time consistently shorter than 5 min. The estimations of subcutaneous glucose concentration during these tests were compared to the concomitant plasma glucose concentrations by using a grid analysis. Three days after implantation ($n = 6$ experiments), 79 estimations were considered accurate, except for five which were in the acceptable zone. Ten days after implantation ($n = 5$ experiments), 101 estimations were accurate, except for one value, which was still acceptable. The sensitivity was around 0.5 nA · mmol^{-1} · l^{-1} on day 3 and day 10. A longitudinal study on seven sensors tested on different days demonstrated a relative stability of the sensor's sensitivity. Finally, histological examination of the zone around the implantation site revealed a fibrotic reaction containing neocapillaries, which could explain the fast response of the sensor to glucose observed in vivo, even on day 10. We conclude that this miniaturized glucose sensor, whose size makes it easily implanted, works for at least ten days after implantation into rat subcutaneous tissue.

Key words: Glucose sensor, subcutaneous tissue.

The aim of a glucose sensor is to provide an accurate continuous measurement of in vivo glucose concentrations. Its potential use for the treatment of Type 1 (insulin-dependent) diabetes mellitus includes the possibility of continuous glucose monitoring, the development of an alarm device for detecting hypoglycaemia or ultimately part of a closed-loop insulin delivery system [1]. Due to the potential hazards if the sensor were implanted in the vascular bed [2], most of the studies have focused on the development of needle-type glucose sensors which, implanted in the subcutaneous tissue, can be easily removed and replaced by the patient [3–11]. Indeed the glucose concentration in subcutaneous tissue closely follows the plasma glucose concentration under stationary conditions [12]. Moreover, the possibility of using subcutaneous glucose concentrations as a signal to monitor blood glucose with a closed-loop insulin delivery system has been clearly established [13]. Development of a needle-type glucose sensor as a step towards the achievement of a clinically useful device requires two further advances: its miniaturization and improvement of its lifespan. Our laboratories have developed a sensor whose size (outer diameter less than 0.5 mm) makes it easily implanted into the subcutaneous tissue. This sensor was evaluated after implantation into the subcutaneous tissue of normal rats, for up to ten days.

Materials and methods

Miniaturized sensor

The sensor consisted of a platinum-iridium wire coated with teflon (0.25 mm outer diameter), except for a 2 mm cavity near its extremity, where glucose oxidase was immobilized on cellulose acetate, reticulated with glutaraldehyde, and covered by a polyurethane layer. The cathode consisted of an Ag/AgCl wire, wrapped tightly around the teflon coated wire. The external diameter of the glucose sensor was therefore 0.45 mm (Fig. 1). The sensor and its in vitro characterization have been described elsewhere [14]. The in vitro characteristics of the 11 sensors used in this study, determined in phosphate buffer at 37 °C before implantation, are shown in Table 1.

Fig. 1. Miniaturized glucose sensor

Sensors were sterilized by dipping them into thimerosal 2.5% thiomersal, Sigma, St. Louis, Mo., USA, [11].

Experimental procedure for the long-term evaluation of the sensor

A simple experimental procedure was used for the long-term assessment of the sensor: the sensor was implanted under halothane anaesthesia into the interscapular subcutaneous tissue of overnight-fasted male normal Wistar rats (250–300 g body weight), through a 16 gauge cannula. The cannula was then removed, leaving the sensor in place secured with adhesive plaster. Between the tests which are described below, the animals were left free-moving in their cages, without polarization of the sensor.

For the recording of the current, the sensor was connected to an amperometric unit (PRG-DEL, Tacussel Electronique, Villeurbanne, France). A run-in period (2 to 6 h) was required to obtain a stable current before performing the glucose test, consisting of an intraperitoneal injection of glucose (30% solution, 1.0 g/kg body weight, or 1.2 g/kg if plasma glucose was lower than 5 mmol/l). Plasma glucose concentration was determined in blood from a tail vein sample with a heparinized Pasteur pipette, at 5 min intervals. A Beckman analyser was used for glucose assay. Eleven different rats were used, each implanted with a different sensor. In seven cases, the tests were performed on different days after implantation (up to 10 days in one rat). In this first set of experiments, the cause for experiment termination was the removal of the sensor by the animal. It was, nevertheless, possible to recognize the sensor implantation site which was sampled for histological examination. In four additional cases, the glucose test was only performed on day 10, the animal being killed after the test. In these cases, the implantation area was fixed with the sensor in Bouin's solution for histological examination. After fixation (10–12 h) the sensor was removed, then longitudinal and transverse slices of specimen were processed for routine histological study in paraffin sections. Thus, we will present the figures obtained on day 3–4 ($n = 6$), on day 10 ($n = 5$) following the implantation, and a longitudinal study of the sensor response evaluated on different days ($n = 7$).

Calculation of the in vivo characteristics of the sensor and data analysis

The in vivo characteristics (sensitivity, extrapolated background current) were determined during an intraperitoneal glucose load. Plasma glucose increased to a plateau, whose duration was usually at least 10 min, long enough to establish equilibration between plasma and subcutaneous glucose concentrations [14]. A two-point calibration procedure previously described [15] was used to transform the recorded current (expressed in nA) into an estimation of the glucose concentration in subcutaneous tissue (expressed in mmol/l): This procedure takes into account the plasma glucose values (in mmol/l) and the corresponding current levels (in nA) in the basal state and at the peak reached during the glucose load. From these values it was possible to calculate, for each individual experiment, an in vivo sensitivity coefficient (SC, in nA $mmol^{-1}\,l^{-1}$) and an extrapolated background current (current in absence of glucose: I_0, in nA). The subcutaneous glucose concentration (SCG) was calculated from the current and the in vivo parameters, according to the equation:
$SCG = [I(t) - I_0]/SC$.

Statistical analysis

A statistical study (regression equation, correlation coefficient) is insufficient for evaluating the accuracy of the glucose concentrations determined from the signal of the sensor, since in addition, examination of clinical significance, taking into account the range of blood glucose concentrations currently observed in diabetes practice, is required. Thus, we supplemented the usual statistical methodology by using the "error grid analysis", proposed by Clarke et al. [16], to evaluate the clinical accuracy of various monitoring systems of blood glucose. This grid is divided into five zones, corresponding on a clinical basis to different degrees of accuracy of glucose estimations. Briefly, values of glucose concentration in zone A are accurate, in zone B, acceptable, and in zones C, D, E, unacceptable because the results would lead to inaccurate and clinically dangerous treatment decisions. This analytical procedure was applied to the data collected during intraperitoneal tests performed at a day 3 and 4 ($n = 6$) or at day 10 ($n = 5$): the estimation of the subcutaneous glucose concentration was plotted against the concomitant plasma glucose concentration. The basal and peak glucose values used for the determination of the sensor in vivo parameters were neither included in this analysis nor in the calculation of regression equation and correlation coefficient, since, by mathematical construction, they are identical to the subcutaneous glucose values.

Results

Figure 2 presents the data (mean ± SEM) for the six experiments (six different animals with a different sensor) performed on day 3 ($n = 5$) or day 4 ($n = 1$). The run-in period (the 2 to 6 h after connection of the sensor to the amperometric unit necessary to obtain a stable current) is not represented. Its duration was not influenced by the duration (in days) of implantation. Following the glucose injection, plasma glucose increased from 4.6 ± 0.7 mmol/l to a peak value of 10.8 ± 0.3 mmol/l. It then decreased

Table 1. In vitro characteristics of the sensors before implantation

	$\Delta I/\Delta C^a$ (nA · $mmol^{-1}\,l^{-1}$)	Linearity range (mmol/l)	Io^b (nA)	$t90\%^c$ (s)
Mean	1.72	22	1.9	190
SEM	0.17	2	0.4	40

mean ± SEM, $n = 11$

[a] $\Delta I/\Delta C$, in vivo sensitivity coefficient:

[b] Io, extrapolated background current (glucose concentration = 0 mmol/l):

[c] t90%, time until 90% of the final steady-state current is reached after switching the sensor from 0 to 5 mmol/l glucose-containing solutions

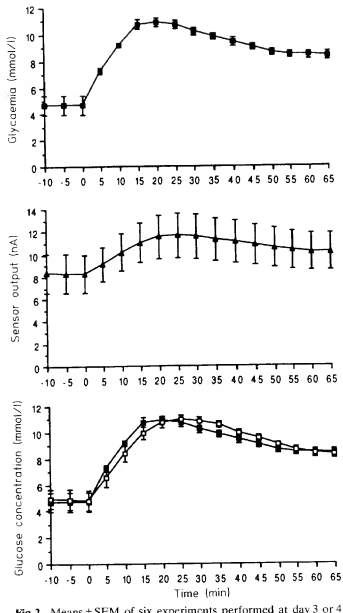

Fig. 2. Means ± SEM of six experiments performed at day 3 or 4 after sensor implantation. Upper panel: plasma glucose concentration (■); middle panel: simultaneous sensor output (▲), lower panel: plasma glucose concentration (■) and estimated subcutaneous glucose concentration (□)

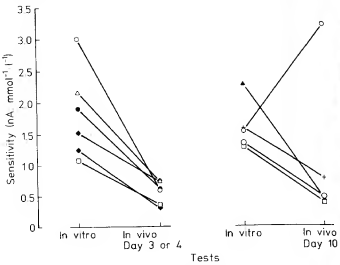

Fig. 3. Individual values of the in vitro sensitivity before implantation and the corresponding in vivo sensitivity on day 3–4 (left panel) or day 10 (right panel) after implantation, determined for each sensor

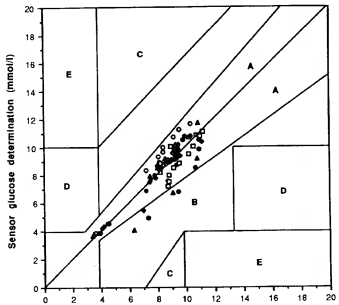

Fig. 4. Error grid analysis for estimation of the accuracy of sensor generated blood glucose values, three or four days after implantation. Zone A: clinically accurate; zone B: acceptable values; zones C, D, E: inaccurate values. Each sensor is represented by a different symbol

slowly after a 10 min plateau to reach a new stable value of 9.0 ± 0.2 mmol/l at 45 min. In the same time interval, the current values, depending on the characteristics of each sensor, rose from 8.3 ± 1.7 nA to 11.7 ± 2.0 nA and then decreased to 10.0 ± 1.7 nA. The in vivo sensitivity coefficient and the background current, calculated for each experiment from the initial and peak values of glycaemia and current, were 0.54 ± 0.08 nA · mmol^{-1} · l^{-1} and 5.8 ± 1.4 nA, respectively. The sensitivity was significantly lower in vivo than that observed in vitro for the same sensors (1.82 ± 0.29 nA · mmol^{-1} · l^{-1}, $p < 0.005$), (Fig. 3, left panel). Subcutaneous glucose concentrations, taking into account the individual in vivo parameters, are represented on the lower panel of Figure 2 with the plasma glucose concentration curve. The lag between the two curves was always shorter than 5 min. Thus, the peak in plasma glucose and in subcutaneous glucose concentrations was observed respectively at 22 ± 3 min and 25 ± 2 min. It must be stressed that no drift in the sensor signal was observed over the duration of these experiments, since subcutaneous glucose concentrations determined at the end of the experiment from the parameters calculated at its beginning were strictly identical with plasma glucose concentrations (8.4 ± 0.3 mmol/l). The correlation between the 79 values of glycaemia and the 79 values estimated from

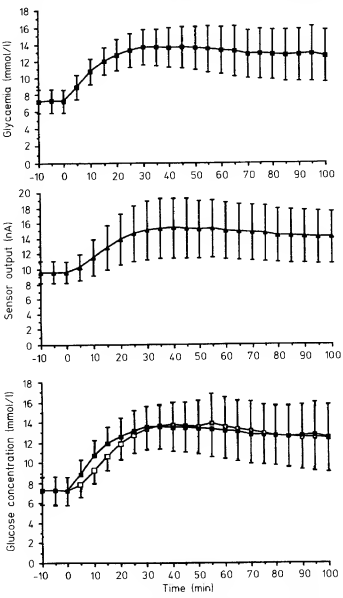

Fig. 5. Mean ± SEM of five experiments performed at day 10 after sensor implantation. Upper panel: plasma glucose concentration (■); middle panel: simultaneous sensor output (▲); lower panel: plasma glucose concentration (■) and estimated subcutaneous glucose concentration (□)

the signal of the sensor was $y = 0.97x + 0.22$ mmol/l, $r = 0.91$, $p < 0.001$. Analysis of these results through the error grid analysis proposed by Clarke yielded 74 values (93.6%) in zone A and five values (6.3%) in zone B (Fig. 4).

Figure 5 represents sensor response obtained during a glucose test performed on day 10 after implantation ($n = 5$). It illustrates the rapid increase in the signal after the glucose injection which was observed in all cases within 2 min. Plasma glucose concentration measured and subcutaneous glucose concentrations estimated from the signal are represented. In these experiments also, subcutaneous glucose concentration determined at the end of the experiment from the parameters calculated at its beginning was identical to the concomitant plasma glucose concentration. After the glucose injection, the signal began to increase with a short lag time (2.0 ± 0.5 min, $n = 5$). The correlation at day 10, between the values of glycaemia and the simultaneous estimates of subcutaneous glucose concentration ($n = 101$), was $y = 0.99x - 0.16$ mmol/l, $r = 0.99$, $p < 0.001$. Analysing these results through the error grid analysis indicated that all values were in zone A, except one value present in zone B near the border of zone A (Fig. 6).

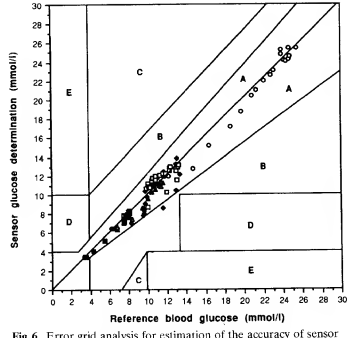

Fig. 6. Error grid analysis for estimation of the accuracy of sensor generated blood glucose values. ten days after implantation

The in vivo background current was 4.2 ± 0.48 nA. Here again, the in vivo sensitivity (1.05 ± 0.55 nA · mmol^{-1} · l^{-1}) was lower than that observed in vitro (1.59 ± 0.18 nA · mmol^{-1} · l^{-1}), except for one sensor (Fig. 3, right panel). Together, the four other sensors yield in vitro and in vivo sensitivities of 1.96 ± 0.30 and 0.60 ± 0.23 nA · mmol^{-1} · l^{-1}, respectively. These figures were similar to those observed with the sensors investigated at day 3.

Figure 7 represents the follow-up study of one sensor implanted for 5 days in a rat, the glucose test being performed on days 1, 2, 3, and 5. Plasma glucose concentration and the current are represented. Figure 8 represents a longitudinal study of the sensor sensitivity. The results of seven experiments are shown, the sensors being implanted for up to ten days. Except for one sensor, for which a major increase in sensitivity was observed from day 5, and whose sensitivity on day 10 is shown in Figure 3, this figure demonstrates the relative stability of the sensor under these experimental conditions.

The histological examination showed a fibrovascular tissular reaction around the site of implantation of the sensor (Fig. 9 a, b). Few inflammatory cells were seen: mainly macrophages, plasma cells and a few polymorphonuclear cells.

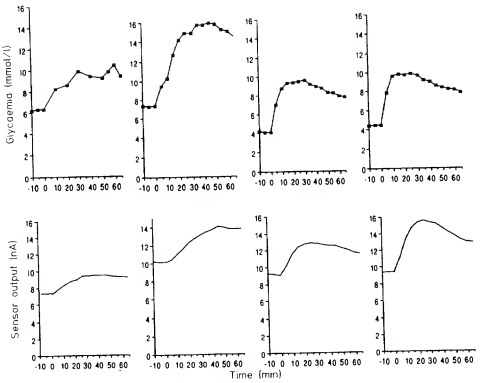

Fig. 7. Follow-up study of one sensor implanted for five days in a rat: plasma glucose concentration (upper panel) and concomitant current (lower panel) on days 1, 2, 3 and 5 after implantation

Discussion

This miniaturized glucose sensor was implanted in the subcutanous tissue of normal rats and its ability to monitor glucose concentration was evaluated up to ten days following implantation. This experimental procedure proved to be useful for the long-term assessment of the sensor. It is simple, non-invasive and reproducible. The increase in plasma glucose concentration following an intraperitoneal injection of glucose and the simultaneous changes in subcutaneous glucose concentration were highly reproducible. The kinetics of glucose variation in the subcutaneous tissue – estimated from the changes in the sensor current during the glucose load – were rapid and followed that of blood, even on day 10, with a lag time always shorter than 5 min. This major finding was clearly demonstrated by using the error grid analysis: on day 3 or 4, only five out of the 79 estimated values from the signal sensor could have been considered as incorrectly estimated compared with the concomitant plasma glucose concentrations, and on day 10 only one of the 101 estimated values could have been considered as such. Even for these six cases, the values fall within acceptable zone B of the error grid analysis. It is impressive to note that this near-identity between subcutaneous glucose concentration and the concomitant glucose level was observed despite the physiological lag between the changes in plasma glucose concentration and those in the subcutaneous glucose. It is compatible with the use of such a sensor for continuous glucose monitoring and even for its use as a part of a closed-loop insulin delivery system, confirming the interest of subcutaneous tissue as a site for glucose sensing [12, 13]. We speculate that the tissue reaction observed around the sensor, namely the presence of capillaries could explain the rapid glucose transfer from the blood to the electrode, and thus explain the improved performances with time reported in this paper.

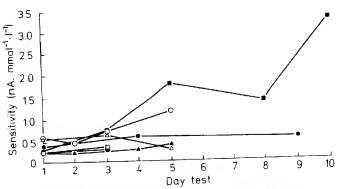

Fig. 8. Longitudinal study of the in vivo sensor sensitivity, up to ten days after implantation ($n = 7$)

In addition, these data suggest that the sensor developed and evaluated in our laboratories functioned consistently for at least 10 days, which is longer than the duration reported by others, who have consistently observed a drift in the sensitivity within less than 5 days [17, 18]. The postulated effect was glucose consumption by the surrounding tissue inflammatory response [19].

In contrast, we did not observe a drift in the sensor sensitivity: except for one sensor, the sensitivity determined in vivo remained relatively stable considering that these experiments were performed in anaesthetized animals, which could vary the glucose supply from blood to the sensor. On the other hand, one must consider that the sensors

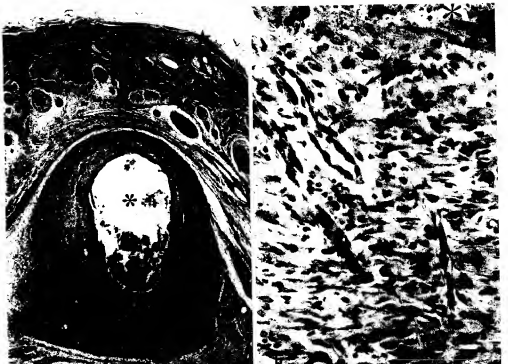

Fig. 9. **a** Transverse section of rat skin and subcutaneous tissue after sensor implantation. A dense granulation tissue surrounds the sensor's area: ★: skin; ✻: sensor's area; →: muscle (haematoxylin and eosin, × 40). **b** Higher magnification of the tissue reaction around the sensor (✻), several small capillaries (→) are visualized (haematoxylin and eosin, × 375)

were not polarized between the tests. It will be necessary to readdress this issue with a continously polarized sensor. Interestingly, the in vivo sensitivity examined on day 10 (except for one sensor), was identical to that observed on days 3–4 and day 10 for sensors with similar in vitro sensitivity. Although the data were obtained with different groups of sensors and do not represent a longitudinal study, this finding suggests that the in vivo sensitivity in subcutaneous tissue remained stable around 0.5 nA · $mmol^{-1} \cdot l^{-1}$ between day 3 and day 10, and are consistent with the data of the longitudinal study.

We observed the development of neovessels around our sensor inside a tissular reaction. It is tempting to speculate that this tissue behaviour was due to the miniaturization of our sensor. In addition, there was no correclation between the in vivo sensitivity and the corresponding in vitro sensitivity of the same sensor (data not shown). This suggests that the in vivo sensitivity is mainly dependent on the in situ environment of the sensor, confirming the need for in vivo calibration.

In conclusion, this paper provides the first evidence that a needle-type glucose sensor miniaturized to a size compatible with clinical use can work for more than 1 week when implanted in rat subcutaneous tissue. The knowledge of the actual duration of the sensor's function is now essential for defining the strategy of its further development, namely towards an implantable or disposable device.

Acknowledgements. We thank Ms. P. Fillatreau for the preparation of the sensors used in this study. This work was supported in part by grants from the National Institutes of Health (DK 30718 to G. Wilson), the Institut National de la Santé et de la Recherche Médicale (CRE 89-90-14 to G. Reach), and l'Aide aux Jeunes Diabétiques.

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Received: 1 August 1991
and in revised form: 4 November 1991

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EXHIBIT D

"THE JOBST PUBLICATION"

Thin-Film Microbiosensors for Glucose−Lactate Monitoring

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A miniaturized device for simultaneous measurement of glucose and lactate levels was produced by means of photopatterning of enzyme-containing photosensitive membrane precursors. This device shows no cross-talk and a lifetime for both the glucose and the lactate sensors of more than 2 weeks when *continuously operated* in undiluted bovine serum. Linear response ranges of up to 40 mM for glucose and 25 mM for L-lactate, in combination with 95% response times of <30 s, were realized. The devices are mass produced by means of thin-film technology on flexible carriers to give catheter-type multisensing devices for in vivo applications. Ex vivo experiments, performed with human volunteers, where the device was continuously operated in an extracorporeal, undiluted, heparinized blood stream for 6 h, gave a correlation of $r > 0.98$ with respect to laboratory techniques. Subcutaneous measurements of glucose levels in pigs were close to the corresponding blood levels obtained without in vivo calibration.

There is a strong demand, especially in the intensive care unit and the operation theater, for miniaturized multianalyte sensing devices that are able to measure simultaneously a set of physiological parameters in vivo or in vitro and that are fast, accurate, cheap, and, of course, reliable.[1,2] These devices might find additional applications in the field of metabolic monitoring, bedside analysis, and clinical analyzers.

Most of the glucose sensing devices intended for in vivo use reported in the literature suffer from the serious drawback that the production processes are rather delicate and therefore difficult to automate. This not only increases the production costs but may also cause serious problems with the reliability of such devices. Therefore, much effort is being focused on the development of biosensors employing established mass production technologies. Screen printing[3] and thin-film[4] technology have already shown success in the manufacture of reliable disposable biosensors.

Furthermore, to create multianalyte devices, the technology employed has to allow the spatially controlled formation of different functional membranes on the corresponding electrodes. Different approaches for the spatially controlled deposition of functional membranes have been reported, including drop-on techniques,[5] ink-jet printing,[6] spray techniques,[7] electropolymerization,[8] lift-off techniques,[9] screen printing technology,[10] enzyme membranes deposited by electrodeposition,[11] and photolithographically patterned enzyme membranes.[12,13]

A straightforward approach is to use membranes that can be directly patterned by photolithography. Of particular advantage is the UV-initiated free radical cross-linking of the polymer directly on the substrate, which allows design of membranes with different physicochemical properties simply by altering the composition of the UV-sensitive membrane precursor or the UV exposure time. To date, however, such attempts have provided a low measuring range[12,13] and, in the case of multienzyme sensors, also suffer from the danger of enzyme mixing.

Finally, for monitoring applications, these devices have to be continuously operated in undiluted whole blood without unacceptable loss in sensitivity.

A thin-film process is presented in this paper that successfully overcomes the aforementioned challenges by immobilizing the enzymes glucose oxidase, lactate oxidase, and catalase in pHEMA−hydrogel membranes and by modification of the platinum anode.

A catalase membrane was created as the topmost layer of this multimembrane setup to prevent cross-talk and the release of the cytotoxic agent hydrogen peroxide[14] to the bulk. The catalase membrane is separated from the oxidase membrane by an enzyme-free diffusion-limiting pHEMA membrane. All mem-

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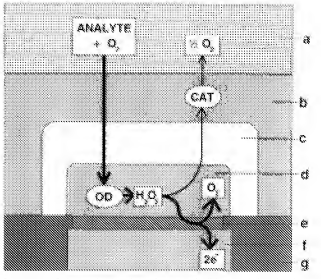

Figure 1. Schematic drawing of sensor buildup and the dominant reaction and transport pathways: a, bulk solution; b, catalase membrane; c, spacer membrane; d, oxidase membrane; e, electropolymerized permselective membrane; f, platinum anode; g, insulation.

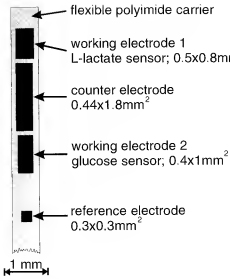

Figure 2. Schematic drawing of the integrated glucose–lactate device. Conducting lines are not shown.

branes were patterned by photolithography. Figure 1 gives a schematic view of the sensor construction and the main reaction and transport pathways.

A miniaturized flexible carrier was chosen to prevent tissue damage in case such a sensor is intended for in vivo measurements. The platinum anode was modified by the deposition of an electropolymerized semipermeable membrane to suppress electrochemical interferences.

EXPERIMENTAL SECTION

Apparatus. A Süss MJB3 mask aligner was used for device preparation and photopatterning of the hydrogels. The electrochemical measurement setup consisted of a home-made SMD bipotentiostat operated in the three-electrode mode, linked to a PC-based data acquisition and actuating program written in Asyst 4.0 (Asyst Technologies Inc.) via an PCL818 ADC board (Advantech). Measurements were performed either in a flow-through cell with 1 mm^2 diameter of the flow channel or by simply inserting the sensor into a magnetically stirred solution in a beaker.

Reagents. Upilex substrates were from ICI (Vienna, Austria); Ti, Pt, and Ag were obtained from Balzers (Liechtenstein); the enzymes glucose oxidase (GOx, EC 1.1.3.4, *Aspergillus niger*, Biozyme GO3A, 360 units/mg protein) and catalase (EC 1.11.1.6, *Aspergillus niger*, Biozyme CATANIF, 3000 units/mg protein) were kindly provided from Biozyme UK; lactate oxidase (LOD, EC 1.1.3.2, *Aerococcus viridans*, Asahi Chem. Ltd., LOD II) was kindly made available by Genzyme UK. Polyimide photoresists are a product of OCG Switzerland. The photoinititator ω,ω'-dimethoxy-ω-phenylacetophenone was purchased from Aldrich. Hydroxyethyl methacrylate (HEMA, >95%) and tetraethylene glycol dimethacrylate (TEGDMA) (75–85%) were from Fluka, pHEMA was from Polyscience, and all other chemicals were of p.a. grade.

A typical hydrogel precursor consisted of 28% pHEMA as polymeric binder, 28% HEMA as reactive monomer, 3% TEGDMA as cross-linker, 40% ethylene glycol as plasticizer, and 1% ω,ω'-dimethoxy-ω-phenylacetophenone as photoinitiator. Dissolution of all compounds gave a clear, colorless solution, which was finally 0.2 μm filtrated. The desired enzymes were added to this precursor solution to give the enzyme membrane precursors, containing up to 5 wt % of the proteins.

Device Fabrication. The thin-film fabrication process of the flexible electrochemical transducers is described elsewhere.[15] One wafer with 60 devices, each of 60 × 0.7 mm^2 size, comprising two platinum working electrodes of 0.4 mm^2 area, one platinum counter electrode, and an Ag/AgCl pseudoreference electrode, insulated by a 1 μm thick photoimageable polyimide dielectricum, is produced on top of a 0.1 mm thick, highly flexible polymer carrier (Upilex). Figure 2 gives a schematic view of this device. The semipermeable membrane was formed by electropolymerization of 1,3-diaminobenzene (3 mM) in phosphate-buffered (pH 7) aqueous solution according to the procedure described by Geise et al.[16] The electropolymerization was performed for at least 6 h on the wafer stage with all working electrodes electrically interconnected. The membrane precursors were applied to the wafers by a spin-on technique without special procedures in any way, identical to that used with common photoresist. The solvent was allowed to evaporate from the formed layers for 0.5 h at ambient temperature. The resulting films were exposed to UV light on the mask aligner through a photomask for typically 30 s up to 2 min in proximity mode. Oxygen exclusion during exposure was realized by argon flushing. The exposed layers were subsequently developed in ethylene glycol/water 1:1 (w/w) with ultrasonic assistance for typically 3 min and rinsed with water.

The multimembrane arrangement was realized by repetition of this basic process with different photomasks and membrane precursors. Finally, the wafer was diced with a circle saw to singularize the devices and bonded to a printed circuit board. The devices may also be sterilized with a γ-radiation dose of 25 kGy from a ^{60}Co source.

In Vitro Measurements. Electrochemical oxidation of hydrogen peroxide was employed as transducing principle. Oxidation of H_2O_2 was performed on both Pt working electrodes at +500

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mV versus the internal Ag/AgCl pseudoreference electrode. In vitro measurements were carried out in 0.1 M phosphate buffer with 0.1 M NaCl (pH 7.4) and undiluted bovine serum. Different glucose and lactate concentrations were realized by addition of the desired amount of 1 M glucose or lithium L-lactate stock solutions, respectively. Oxygen concentrations were decreased by addition of sodium dithionite, while oxygen tension was monitored simultaneously with a home-made thin-film Clark-type oxygen sensing device.[17] Measurements at very low oxygen concentrations were realized by addition of a surplus of dithionite and monitoring while diffusion of oxygen from the surrounding air increased the oxygen level of the test solution.

Ex Vivo and in Vivo Experiments. For ex vivo measurements, the flow cell was combined with a SMD bipotentiostat within one metal housing of 85 × 25 × 25 mm^3 to minimize electromagnetic interferences. Ex vivo blood monitoring with human subjects was performed by placing the flow-through cell into the sampling line of a so-called continuous ambulatory blood sampler.[18] The sampling method is based on a double-lumen catheter for extracorporeal blood heparinization and an automatic fluid sampler. The double-lumen catheter (18 gauge × 45 mm, B. Braun Melsungen AG, Melsungen, Germany) was placed in a peripheral vein. The inner lumen of the double-lumen catheter was connected to a 10 mL syringe containing heparin solution (2000 IU Novo Nordisk, Bagsvaerd, Denmark). Heparin was infused at a rate of 7 μL/min by a piston pump. The outer lumen of the double-lumen catheter was connected to a roller pump. A needle movable in two directions supplied 56 cooled vacuum tubes with the collected blood. The roller pump rate was adjusted to 200 μL/min to realize a sampling volume of 1.5 mL/vacuum tube within 7.5 min.

The ex vivo experiment was performed with a healthy male subject (age 25 years, 96 kg weight). Informed consent was given by the volunteer. After a 12 h overnight fast, the subject assumed a supine position over 6.5 h, and an intravenous glucose tolerance test (IVGTT), followed by an oral glucose tolerance test (OGTT), was then performed. The duration of the experiment was limited to 6.5 h for the convenience of the volunteer. After 30 min rest, at time −15 min, the double-lumen catheter was inserted in an antecubital vein and connected to the blood sampling device. A butterfly (22 gauge) needle was inserted in a dorsal hand vein for the injection of glucose and insulin. Then, 250 mg/kg glucose was injected as 40% solution at time zero, and 0.02 units/kg regular insulin (Novo Nordisk) was injected 20 min later. At time 180 min, 150 g of glucose was given orally. Whole blood glucose was measured from the continuously sampled vacuum tubes (Cobas Mira, Switzerland). L-Lactate determinations were done with the LDH method. Before and after the measurement, the glucose−lactate device was one-point calibrated with a protein-free buffer solution containing 5 mM glucose and 2 mM L-lactate. The measured sensitivities before the experiment were applied to the sensor currents of the experiments for calculation of glucose and lactate levels.

Venous blood monitoring in animal experiments was done with a glucose−lactate device mounted, together with a 0.3 mm o.d. stainless steel cannula, in an 18 gauge catheter (Braun Melsungen). Heparin solution (1000 IU/mL) was perfused through the steel cannula at a flow rate of 0.3 μL/min, while venous blood was pumped through the catheter at a flow rate of 10 μL/min. Heparin supply and blood withdrawal were done with a roller pump equipped with two tubes of different inner diameter in order to realize the desired flow rate ratio of 100:3. Again, one-point precalibration was used in this experiment. Since the sensors were at body temperature during the experiment but were calibrated at ambient temperature, the calibration factors were multiplied by a factor of 1.4, which corresponds to a temperature difference of 15 K and a temperature coefficient of 2.3%/K.

The experiment was performed with a female pig of 15 kg weight. The animal was anesthetized with thiopental/halothane. A catheter placed in an ear vein was used to obtain blood samples for subsequent analysis and also for intravenous administration of glucose and heparin. The monitoring catheter was placed in the vena jugularis and immediately after application was equipped with the sensor and the inner tube for heparin supply.

A second glucose/lactate device was placed subcutaneously near the sternum. Application was done by inserting an 18 gauge steel cannula through the fatty tissue over a distance of 4 cm, inserting the device into the front end of the cannula, and removing the cannula. At time 65 min, 10 mL of 33% glucose solution (220 mg/kg) was administered intravenously. At time 140 min, a dose of 2.5 IU/kg regular insulin (Novo Nordisk) was injected intravenously.

Analysis of the blood samples was done immediately after withdrawal. Glucose analysis was performed with Companion2 (Medisense) and HemoCue B glucose (HemoCue, Sweden). Analysis for L-lactate was done with the Biosen5020L (Analytical Medical Instruments, Vienna, Austria).

RESULTS AND DISCUSSION

Fabrication Technology. PolyHEMA is advantageous as a membrane material because of its well-known blood compatibility,[19,20] its high mechanical strength in the swollen state, and the fact that various photoinitiators are available for the photoinduced cross-linking of methacrylic systems. Additionally, photopatternable precursor solutions can be made with enzyme-compatible solvent mixtures. Furthermore, physicochemical membrane properties can be varied over a broad range by varying of precursor composition and cross-linking conditions.

The handling procedure of the enzymatic and nonenzymatic hydrogel precursors is compatible to a large extent with common thin-film technology processes. Nevertheless, there are two drawbacks of this system with respect to compatibility with thin-film technology:

First, oxygen has to be excluded during UV exposure, since molecular oxygen inhibits the free radical-initiated polymerization and cross-linking process. This can easily be achieved by nitrogen flushing of the wafer during UV exposure.

Second, the membrane precursor is not solid after evaporation of the solvent, but it is highly viscous because of the presence of monomer and plasticizer. The presence of plasticizer during the

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photo-cross-linking process allows the cross-linking to be performed above the glass transition temperature of the formed gel, which ensures high mobility of the reaction partners. This is advantageous in order to get high process speed and sufficient cross-linking.

But because of the liquid nature of the layers, a contact exposure, which is common in thin-film technology, where the substrate is pressed against the photomask, can only be done by separating the photomask from the substrate by some UV-transparent foils.[21] Since the application of such sheets causes some problems with the reproducibility and reliability of the whole process, we decided to employ proximity exposure, where the photomask is separated by a few hundred micrometers from the substrate.

A resolution of ~10 μm can be obtained in hydrogel membranes of 4 μm thickness.

Membrane thickness is easily varied between 1 and 10 μm by proper adjustment of the membrane precursor viscosity. Typically, membranes with a thickness of 4–6 μm are employed in this work. Electropolymerization of the semipermeable membrane can be done at the wafer stage and therefore presents no bottleneck for the mass production of these thin-film devices.

Device Performance. Oxidase-based biosensors without a hydrogen peroxide decomposing top membrane emit hydrogen peroxide to the bulk solution, where it accumulates, depending on the exchange rate of the bulk solution. This accumulation induces according to Fick's first law an increase in sensor current. Simultaneously, substrate and oxygen are depleted from the bulk solution, decreasing the signal. Therefore, sensor reading is influenced by the flow speed of the bulk solution. One way to circumvent this problem is to balance these two processes by proper choice of membrane materials and improved sensor design.[22] Such devices have been shown to display a stir rate-independent reading, and even signal stability for stopped flow is reported.[23]

However, one should keep in mind that this feature is the result of two balanced processes and that the relative rates of these processes are dependent on the transport (diffusion, active transport in tissue) and reaction (catalase activity of tissue) properties of the bulk. This means that a device with virtually no flow dependency in a beaker may respond with a different sensitivity when operated in tissue.

This analyte-dependent behavior may partly explain the numerous reports in the literature where significant differences between in vitro and in vivo sensitivities are described.[24]

Our approach to minimize this problem is to eliminate the hydrogen peroxide accumulation by top-coating the device with a catalase membrane and to keep the analyte consumption low by proper diffusion limitation.

However, since a minimal sensitivity is necessary for reliable measurements, it is highly desirable to optimize the sensitivity versus analyte consumption ratio. This ratio, which is called efficiency, is expressed as the ratio of charge passing the electrode to the total charge which is nominally converted in the enzymatic reaction. Since efficiency is considerably decreased when an oxidase membrane is directly coated with a catalase membrane, we introduced the pHEMA–hydrogel spacer membrane between them to increase the diffusion resistance of hydrogen peroxide toward the catalase membrane.

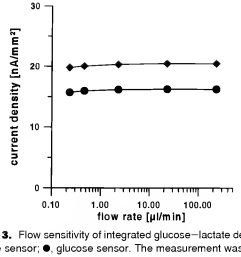

Figure 3. Flow sensitivity of integrated glucose–lactate device: ♦, L-lactate sensor; ●, glucose sensor. The measurement was done in phosphate-buffered saline containing 5 mM glucose and 2 mM L-lactate.

The flow sensitivity of a glucose–lactate device with such a three-membrane setup is shown in Figure 3. Since the measurement was done in a 1 mm^2 cross-sectional area flow channel, the flow rates indicated correspond to flow velocities of millimeters per minute. The current of both sensors is decreased by only 3% when the flow rate is reduced 3 orders of magnitude from 240 μL/min to 0.24 μL/min. The sensitivities of the sensors can be varied over wide ranges (2–10 nA mM^{-1} mm^{-2} for glucose and 5–30 nA mM^{-1} mm^{-2} for L-lactate) by proper choice of membrane thickness and by alteration of the hydrogel precursor composition. For example, L-lactate sensor sensitivity is increased 3-fold and glucose sensor sensitivity is increased 2-fold upon reducing exposure time from 2 to 1 min and increasing the plasticizer content of the prepolymer mixture from 40% to 60%. Relative standard deviations of the sensitivities of flexible devices which were made in the same batch were calculated to be 3.1% (n = 10) for the glucose sensors and 3.2% (n = 10) for the lactate sensors. Hydration of the device proceeds at a faster rate for thin membranes. More than 95% of the final steady state current, caused by the endogenous glucose and L-lactate of the serum, is reached within 5 min (see Figure 4). This figure also illustrates the absence of cross-talking and the fast response of the device. Base current declines below 1 nA mm^{-2} within 30 min, which enables one-point calibration.

The influence of oxygen concentration on glucose reading is shown in Figure 5 for different glucose concentrations. At an oxygen partial pressure of 20 mmHg, which represents the lower physiological level in tissue, the linear measuring range still covers the range of physiological glucose levels. The ratio of oxygen versus glucose sensitivity derived from this measurement is 750.

In view of the general lack of widely accepted parameters for the expression of biosensor performance, we suggest the use of this parameter for the characterization of conventional oxidase-based biosensors whose linear working range is limited by an oxygen deficit. It gives a definite relationship between saturation currents, linear range, and oxygen concentration, and it is nondimensional.

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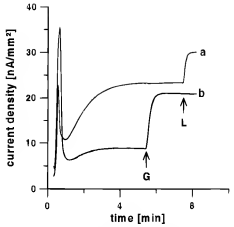

Figure 4. Run-in behavior of an integrated glucose−lactate device which was stored dry in ambient atmosphere. At time zero, the device was inserted into undiluted bovine serum. G, Increase of glucose concentration by 5 mM; L, increase of L-lactate concentration by 1 mM; line a, L-lactate sensor; line b, glucose sensor.

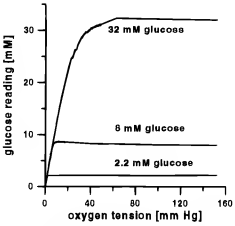

Figure 5. Oxygen dependency of glucose reading.

The influence of interferences was tested with a device that was already continuously operated for 2 days in undiluted bovine serum prior to taking measurements. The concentrations of the interferences tested reflect the upper physiological level. Only paracetamol at the toxic level of 2 mM gave a pronounced increase in sensor reading. Nevertheless, the error in reading is less than 0.5 mM glucose and 0.2 mM L-lactate, respectively, as can be seen in Figure 6. Of particular interest is the very slow response toward paracetamol. The response time of ~5 min can also be observed with electrodes covered only by the semipermeable membrane. The interference becomes negligible when measurement is carried out with these electrodes in batch mode in a clinical analyzer. The temperature coefficient of both the glucose and the lactate sensors is 2.3%/K. This value matches the value of the temperature dependence of diffusion. This is expected since the device works under conditions of mass transfer limitation within the sensor membranes. Therefore, this value should be independent of the nature of the test solution.

Changes in device parameters with continuous operation in undiluted bovine serum for 3 weeks at ambient temperature are shown in Table 1. The useful operational lifetime of the devices is typically more than 2 weeks.

Ex Vivo and in Vivo Monitoring. The well-established continuous blood withdrawal technique by means of a double-lumen catheter and on-line dilution of whole blood with heparin[25] has the serious drawback that the real dilution factor is dependent on hematocrit and therefore requires a calibration with an independent method or hematocrit determination. To prevent such errors, we used a small flow of concentrated heparin solution, which causes a maximum dilution of 3%.

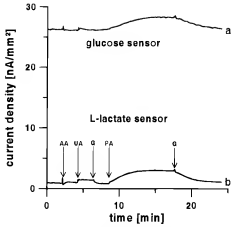

Figure 6. Influence of interferences on sensor reading. The integrated glucose−L-lactate sensor was exposed to 5 mM glucose solutions spiked with different interferences: AA, 0.2 mM ascorbic acid; UA, 0.5 mM uric acid; G, no interfences; PA, 2.0 (!) mM paracetamol; line a, glucose sensor; line b, L-lactate sensor.

Table 1. Results of Long-Term Experiment

	sensitivity to substance (nA mM^{-1} mm^{-2})				upper limit of linear range[a] (mM)		saturation current (nA mm^{-2})	
			uric					
day	glucose	lactate	acid	paracetamol	glucose	lactate	glucose	lactate
0	3.95	11.2	<0.1	<0.1	>40	29	342	318
7	4.58	12.1	1.2	1.5	>40	29	337	325
14	5.18	14.0	1.2	1.0	>40	26	380	328
21	5.03	13.4	4.0	1.2	>40	20	407	290

[a] Deviation from linearity > 10%.

The result of an IVGTT/OGTT experiment is shown in Figure 7. The sensor reading closely follows the laboratory results throughout the duration of the experiment. Sensitivities measured before and after the experiment according to the procedure given in the Experimental Section were 4.55 and 4.40 nA mM^{-1} mm^{-2} for glucose and 30.7 and 29.1 nA mM^{-1} mm^{-2} for L-lactate. Error grid analysis[26] of the glucose values shows that all values, except the one immediately after the intravenous administration of glucose, lie in zone A (clinically accurate, Figure 8). The correlation coefficient of the linear least-squares fit of this data set is $r = 0.98$. Lactate sensor reading and laboratory results of this experiment are shown in Figure 9. Supported by the results of such IVGTT/OGTT experiments with ex vivo flow-through devices,[27] we assume that the deviation between sensor reading and laboratory results is caused by an error in the off-line lactate determination.

Since the high blood withdrawal rates used in this experiments are not acceptable for monitoring applications, in an animal

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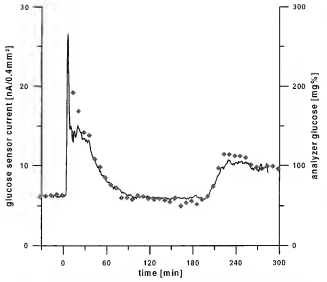

Figure 7. IVGTT–OGTT experiment with human volunteer: —, glucose sensor current; ♦, laboratory glucose. For experimental details, see text.

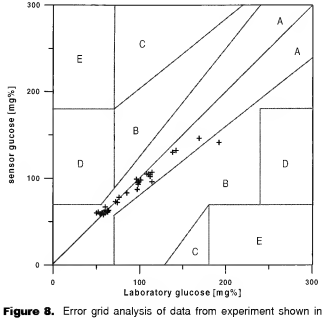

Figure 8. Error grid analysis of data from experiment shown in Figure 7. Total number of points, 39; points in zone A, 38; points in zone B, 1.

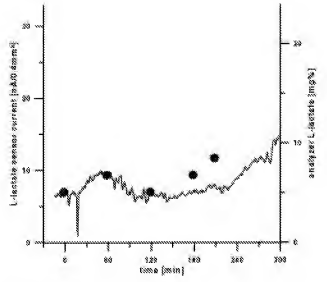

Figure 9. Same experiment as shown in Figure 7: —, lactate sensor current; ●, laboratory lactate.

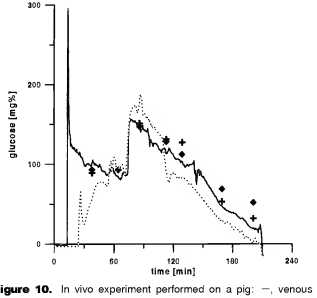

Figure 10. In vivo experiment performed on a pig: —, venous glucose sensor reading; •••, subcutaneous glucose sensor reading; +, Companion2 glucose values; ♦, Hemocue B glucose values. For experimental details, see text.

experiment we evaluated the feasibility of a monitoring scheme with the sensor mounted in a catheter, which allows reduction of the flow rate to 14 mL/day without an unacceptable delay. Additionally, a device was placed subcutaneously in the pig, which is the most accepted application site for hypoglycemia home monitoring.

The results of this animal experiment are shown in Figure 10. Again, a close correlation between venous sensor reading and off-line values can be seen. Error grid analysis gives 100% zone A at $n = 7$. After a 30 min run, the subcutaneous sensor reading approaches venous glucose values. The sensor responded very fast to the intravenous glucose load. There was no time lag relative to the venous sensor reading. Sensitivities before and after the experiment were identical within the limits of experimental error. The correlation coefficient of venous versus subcutaneous sensor readings, starting at time 30 min, is $r = 0.95$. The sharp decrease of its sensitivity at time 110 min may be caused by a change in the position of the sensor in the subcutaneous tissue. An encouraging observation made in this preliminary experiment is that the in vivo sensitivity of the glucose device was of the order of the in vitro sensitivity. Clinical studies to evaluate the possibility of precalibration for short-term subcutaneous glucose sensing are underway and will be published in a forthcoming paper.

Sensors with the same membrane buildup but with an unmodified platinum anode showed the well-known behavior of a steady decrease in sensitivity when operated in real samples.[15] Most often, this decrease in sensitivity is attributed to improper biocompatibility of the sensor surface.[28] The fact that oxygen transducing devices employing gas-permeable membranes to protect the electrodes show excellent stability even in whole

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